Neurobiological Investigation of Salience Processing in the Pre-psychotic State

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We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time…

T. S. Eliot, 1942

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Summary

Schizophrenia is a severe psychotic disorder characterized by distortions of reality. Our current understanding of schizophrenia still remains fragmented and the cause of the disorder has not yet been determined. Recent research indicates that it may be possible to diagnose an at-risk condition prior to the manifest phase of schizophrenia. This state is predominantly characterized by attenuated psychotic symptoms and disturbances of perception and thought. An oft-described experience in individuals at risk is a sensory overload with a growing sense that events and things around them have a hidden meaning. The salience hypothesis provides a powerful heuristic framework that explains both neurobiological disturbances and the subjective experience of these phenomena. Accordingly, a dysregulated, hyperdopaminergic state leads to an inadequate assignment of importance to events or internal representations.

Depending on the nature of how a stimulus is evaluated, two differing concepts have been proposed: motivational salience and proximal salience. The former drives goal-directed behavior by attaching a tag to a cue according to its association with reward or punishment, the latter takes place once a stimulus is evaluated in the context of interoceptive awareness.

The prevailing motive of this thesis was to reveal the neurobiological mechanisms of these two concepts using functional magnetic resonance imaging. Considering that proximal salience may be studied indirectly via functional connectivity analysis of the salience network, and motivational salience via reward-based processing, two experimental approaches were followed: Exploring the intrinsic functional connectivity between salience-relevant networks; and investigating motivational salience processing using a delayed incentive paradigm with monetary rewards.

Proximal salience is hypothesized to be mediated through the salience network, which initiates the recruitment of brain regions relevant for processing salient stimuli but importantly also enables switching between the so called default mode and task-positive network. In the healthy brain the activity between the networks are anticorrelated, which possibly reflects competition between the processing of external and internal information processing. The findings revealed that this typically observed antagonistic relationship was absent in the risk-state for psychosis. This may reflect a confusion or misperception of internally and externally focused states.

The second study provides evidence for a latent reward associated dysregulation, which is associated with pre-psychotic symptoms. The putatively dopaminergically mediated higher activation in striatal and insular regions during anticipation of incentive cues in those subjects may reflect an abnormal processing of potential future rewards which in turn, according to the aberrant motivational salience theory of psychosis, may predispose a person to develop full expression of psychotic symptoms.

This work provides compelling evidence for the aberrant proximal salience processing as well as a latent dysregulation of motivational salience processing playing an important role in the development of psychotic disorders. These findings provide further insight into illness susceptibility, and consequently into the neuropathophysiological mechanisms in the development of psychotic disorders.

Zusammenfassung

Die Schizophrenie ist ein psychisches Störungsbild, die mit einem tiefgreifenden Realitätsverlust, den sogenannt psychotischen Symptomen, einhergeht. Der gegenwärtige Kenntnisstand über die pathophysiologischen Abläufe, die zu einer schizophrenen Erkrankung führen können, bleibt bis heute bruchstückhaft. Jüngste Forschungsergebnisse zeigen gleichwohl, dass ein Risikostadium diagnostizierbar ist, welcher dem Ausbruch der Erkrankung vorausgeht. Dieses ist überwiegend durch abgeschwächte psychotische Symptome, sowie durch Störungen der Wahrnehmung und des Denkens charakterisiert. Eine häufig beschriebene Erfahrung von Betroffenen ist das Auftreten von sensorischer Überflutung, welche mit einer zunehmenden Überzeugung einhergeht, dass vordergründig irrelevante Ereignisse eine versteckte Bedeutung in sich tragen. Die sogenannte Salienzhypothese bietet ein heuristisches Erklärungsmodell, welcher zufolge ein dysregulierter dopaminerger Zustand dazu führt, dass Ereignissen inadäquate Wichtigkeit zugesprochen wird.

Abhängig davon, wie ein Stimulus bewertet wird, wurden zwei Konzepte formuliert; jenes der motivationalen und der proximalen Salienz. Ersteres steuert dabei zielgerichtetes Handeln, in dem ein Stimulus zuvor mit Belohnung oder Bestrafung assoziiert wurde und damit zu gesonderter Bedeutung gelangt. Demgegenüber erfolgt proximale Salienzzuschreibung im Kontext der Wahrnehmung interozeptiver Vorgänge.

Ziel der vorliegenden Arbeit war es, mittels funktioneller Magnet Resonanz Tomographie die neurobiologischen Mechanismen dieser zwei Konzepte und deren Relevanz für die Entwicklung psychotischer Störungen zu untersuchen. Unter der Annahme, dass proximale Salienz indirekt via funktioneller Konnektivitätsanalyse des sogenannten Salienznetzwerkes untersucht werden kann und

motivationale Salienz durch die Analyse der neuronalen Belohnungsverarbeitung, wurden zwei Untersuchungsansätze verfolgt: Die Untersuchung intrinsischer funktioneller Konnektivität zwischen salienzrelevanten Netzwerken und neuronaler Verarbeitung von monetären Anreizen mit verzögerter Belohnung.

Es wird angenommen, dass das Salienz-Netzwerk einerseits die Rekrutierung von Gehirnarealen initiiert, welche relevant sind, um saliente Stimuli zu verarbeiten und andererseits die Aktivierungszustände des Default-Mode und des taskpositiven Netzwerkes reguliert. Im gesunden Gehirn widerspiegelt die antagonistische Aktivität dieser Netzwerke auf ein Konkurrenzverhältnis zwischen nach aussen und nach innen gerichteter Informationsverarbeitung. Die Befunde zeigen, dass im Risikostadium psychotischer Erkrankung diese antagonistische Beziehung absent ist und weisen damit auf eine Konfusion internaler und externaler Zustände hin.

Die zweite Studie erbringt den Nachweis einer latenten Dysregulation der Belohnungsverarbeitung. Entsprechend der motivationalen Salienzhypothese könnte die mutmasslich dopaminerg vermittelt stärkere Aktivierung striataler und insulärer Gehirnregionen bei der Präsentation belohnungsrelevanter Anreize bei Personen mit stärker ausgeprägten prä-psychotischen Symptomen dafür verantwortlich sein, dass Stimuli eine erhöhte Salienz zugesprochen wird.

Die vorliegende Arbeit bietet Indizien, dass mit dem prä-psychotischen Stadium eine Dysregulation proximaler sowie latent motivationaler Salienzverarbeitung einhergeht und damit eine wesentliche Rolle in der Entwicklung psychotischer Störungen zugeordnet werden kann. Die Befunde ermöglichen ferner bedeutende Einsichten in die Hintergründe der Krankheitssuszeptilität und die möglicherweise zugrundeliegenden neuropathophysiologischen Mechanismen psychotischer Störungen.

Original research articles included in this doctoral thesis

Study I

Aberrant coupling within and across the default-mode, task-positive, and salience network in subjects at risk for psychosis.

Wotruba D.[1-3], Michels L.[1,4], Buechler R.[1,2], Theodoridou A.[2,5], Gerstenberg M.[1,2], Kollias S.[1], Roessler W.[2,3,7], Heekeren K.[2,5]. *Schizophrenia Bulletin* (2014)

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Study II

Symptom dimensions are associated with reward processing in unmedicated persons at risk for psychosis.

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Contents

Chapter 1

Theoretical background

1.1. Introduction

Schizophrenia is a chronic mental disorder that affects about one percent of the world's population, and continues to be one of the most severe and debilitating disorders (Rössler, Salize, van Os, & Riecher-Rössler, 2005). Affected persons suffer from cognitive disturbances and a variety of symptoms, commonly categorized as negative and positive symptoms. Negative symptoms comprise blunting of affect and decreased ability to initiate thoughts and ideas. Positive symptoms are features of psychosis and include hallucinations (i.e. hearing voices not heard by others), delusions (believing that other people are reading their minds, controlling their thoughts, or conspiring against them) or disorganized thinking (MacDonald & Schulz, 2009; Möller, 2004).

Our current understanding of schizophrenia still remains fragmented and decades of intense effort in research cannot yet determine the cause of the disorder so far. Yet, proceeding from Kraepelins concept of *dementia praecox*[1], epidemiological and neurobiological findings lead to the proposition of a neuro-developmental approach to the classification of schizophrenia (Murray, O'Callaghan, Castle, & Lewis, 1992). Accordingly, the illness is hypothesized as being a result of an early brain insult affecting brain development, with psychosis as a late, but potentially preventable stage of illness (Insel, 2010; Rapoport, Giedd, & Gogtay, 2012; Tandon, Nasrallah & Keshavan, 2009).

Therefore, some research focused on different stages of the illness revealing for instance a progressive gray matter decline during the early phases of illness and higher treatment responsiveness during the first episode (De Koning et al., 2009). Moreover, retrospective accounts

[1] The term refers to a chronic, deteriorating psychotic disorder characterized by rapid cognitive disintegration. It was first used in 1891 by the Czech neurologist Anrnold Pick, and popularized later by Emil Kraepelin (1856–1926), and reconceptualized when Freudian perspectives became influential. This lead to Eugen Bleuler's term *schizophrenia*, which rose in prominence as an alternative to Kraepelin's concept (for a review consider Hoenig, 1983).

of *prodromal*[2], early illness signs have been documented in the vast majority of cases (Correll, Hauser, Auther, & Cornblatt, 2010). The importance of studying people presenting with potentially prodromal symptoms has been increasingly recognized, considering impressive clinical benefits of preventive interventions in psychosis (Phillips et al., 2005; Yung et al., 2003, 2008). Whether defined as potentially prodromal, pre-psychotic or as at-risk mental state (Schultze-Lutter, Schimmelmann, & Ruhrmann, 2011) this stage is predominantly characterized by a variety of attenuated psychotic symptoms and subtle, self-experienced disturbances of perception and thoughts (e.g. such as bizarre ideas), reduced social functioning and cognitive decline (often apparent by reduced school performance) (Addington & Heinssen, 2012; Andreasen, Pressler, Nopoulos, Miller, & Ho, 2010; Salokangas & McGlashan, 2008).

These symptoms appear five to six years prior to the onset of frank psychotic symptoms (Schultze-Lutter, Ruhrmann, Berning, Maier, & Klosterkötter, 2010), while typically psychosis emerges in late adolescence or early adulthood, when the pre-frontal cortex is still developing (Paus, Keshavan, & Giedd, 2008). Insel (2010) speculated that this late stage of brain maturation involves a careful calibration of excitatory-inhibitory balance in the cortex. He pointed out that one relevant modulator of this balance is dopamine. Indeed, dopamine dysregulation remains a cornerstone in our emerging understanding of the etiopathogenesis of schizophrenia. Indirect evidence is provided by the clinical effectiveness of antipsychotic drugs that block dopamine receptors (Howes, Fusar-Poli, Bloomfield, Selvaraj, & McGuire, 2012; Howes & Kapur, 2009).

An often described experience during the prodrome to psychosis is a sensory overload, with a growing sense that things and events around

[2] The term prodrome depicts a state with early unspecific symptoms but can only be diagnosed *restrospectively* after manifestation of illness (Schultze-Lutter et al., 2011).

the individual have an important hidden meaning, which may create a new world, where everything gets a new meaning, thus representing clinical features of an impending onset of psychosis (Winton-Brown, Fusar-Poli, Ungless, & Howes, 2013). According to the *salience hypothesis* of psychosis, these phenomena might be explained by dopaminergic dysfunction, where an aberrant assignment of importance to environmental events and internal representations would lead to such symptoms (Kapur, Mizrahi, & Li, 2005; Mishara & Fusar-Poli, 2013; Winton-Brown et al., 2013).

There is general agreement for the central role of dopamine in reward processing (Bromberg-Martin, Matsumoto, & Hikosaka, 2010), which has been studied extensively in schizophrenia (Andreas Heinz & Schlagenhauf, 2010). It has been suggested however, that dopamine may not only code for rewards, but may also reflect general salience (Flagel et al., 2011; Ungless, 2004), putatively mediated through functionally distinct subgroups of dopamine neurons (Bromberg-Martin et al., 2010; Matsumoto & Hikosaka, 2009). Accordingly, depending on the nature of how a stimulus is evaluated, two differing concepts have been proposed: reward related *motivational salience* vs. the more fundamental concept of *proximal salience* (Palaniyappan & Liddle, 2012).

Motivational salience drives goal-directed behavior by attaching a tag to a cue according its association with reward or punishment. In schizophrenia chaotic and stimulus independent release of dopamine would result in inadequate attention to trivial events (Kapur, 2003), i.e. a statement of a TV reporter on the growing ozon layer hole, which then might gain motivational power to drive bizarre behavior, such as shielding of the apartment walls with metal panels. *Proximal salience,* on the other hand, is taking place once an internal or external stimulus is evaluated in the context of interoceptive awareness. Effective cognitive control requires successful suppression of distractors (e.g., spontaneous internal thoughts). Psychotic symptoms would arise through inappropriate salience attribution to bodily sensation or a stimulus-independent thought. This will result in updating

expectations, which might enhance the state of uncertainty and ultimately lead to an inner process acquiring unwarranted causal significance (i.e. enhanced and inappropriate attention to ones own body odor might lead to believe that this is caused by the neighbor intentionally trying to empoison them) (see for a review Palaniyappan & Liddle, 2012).

Both concepts provide a powerful heuristic framework that explains both the neurobiological findings in schizophrenia and the patients' subjective experience of symptoms (Tost, Alam, & Meyer-Lindenberg, 2010), but crucially also that of clinical phenomena such as delusional ideas as well as disturbances of motivational (negative) symptoms experienced by subjects at-risk for psychosis. Consequently, aberrant salience processing could play a decisive role in the developing overt symptoms seen in schizophrenia.

Therefore, the aim of this dissertation was to shed light on the role of salience processing in the development of psychotic disorders by the following outline:

Firstly, some aspects of different approaches to diagnosing the at-risk state for psychosis are addressed, and this is followed by a description of the salience hypothesis of schizophrenia. The salience network is associated with the concept of proximal salience. Consequently, the dopamine hypothesis of schizophrenia will be related to reward processing and its putative role for aberrant motivational salience processing in psychotic disorders. **Chapter 2** highlights the study sample and addresses the methods used for this thesis: (1) resting-state functional magnetic resonance imaging (fMRI) to study functional connectivity of the salience network and (2) task-based fMRI to investigate reward processing. A detailed description of the applied methods in the experiments follows in the methods sections (chapter 4.3 and 5.3). After the formulation of the main aims of this dissertation (**chapter 3**), the empirical work is included in **chapters 4 and 5. The first study** (Aberrant coupling within and across the default-mode, task-positive, and salience network in subjects at risk for psychosis)

addresses the proximal salience by studying it indirectly through comparing the functional connectivity of the salience network in two symptomatically different at-risk groups and healthy controls, while the focus of the **second study** (Reward processing in unmedicated persons at-risk for psychosis) is exploring putative disturbances of reward-based, motivational salience in the at-risk-stage for psychosis. **Chapter 6** highlights the main limitations and conclusions that can be drawn from these studies.

1.2. Risk for psychosis

The last two decades of research into the prodromal phase of psychosis have revealed promising insights into the mechanisms underlying schizophrenia and other psychotic disorders. In particular because investigation of subjects at the beginning of illness allows researchers to examine subclinical manifestation of psychosis reasonably free of the confounding consequences of clinical disorders (such as neurodegenerative progress of disease, institutionalization and treatment, particularly with antipsychotics) (Fusar-Poli, McGuire, & Borgwardt, 2012). To explore vulnerability to psychosis, researchers employ various strategies to identify the at-risk stage of psychosis. The most frequently used terms are at-risk mental state (ARMS), clinical high-risk state (HR) based on basic symptoms, ultra-high risk state (UHR) or attenuated psychosis syndrome (APS) (Schultze-Lutter et al., 2011). APS was controversially debated as a new diagnostic category in the most recent issue of the diagnostic and statistical manual of mental disorder (DSM-V) by the *American Psychiatric Association* (Fusar-Poli & Yung, 2012; Tsuang et al., 2013; Yung et al., 2012).

Two commonly used sets of criteria to diagnose the risk-state of psychosis are the HR and UHR criteria, where the former is assumed to characterize the early prodromal phase, the latter the late prodromal phase (Fusar-Poli et al., 2013; Klosterkötter, Schultze-Lutter, Bechdolf, & Ruhrmann, 2011). Both are used in the present study and thus deserve some elaboration.

UHR criteria are fulfilled by the presence of subclinical positive symptoms or a state-trait vulnerability that covers a high genetic risk plus a marked decline of the psychosocial functioning level (see Table 1). The risk-associated positive symptoms are APS or brief, limited intermittent psychotic episodes (BLIPS). APS include subthreshold positive symptoms such as hallucinatory experiences assessed at the extremes of normal limits or delusional (often persecutory) ideas that are easily dismissed and do not affect behavior to a significant extent (Yung & Mcgorry, 2007). BLIPS on the other hand describe transient frank psychotic symptoms, lasting less than a week and resolving themselves spontaneously.

HR criteria or basic symptoms are subtle, often only self-perceivable disturbances in cognition, thought and perception, which are clustered in two partially overlapping subsets relating to cognitive-perceptive symptoms (COPER) and cognitive disturbances (COGDIS) (see Table 2). Basic symptoms are clearly distinct from attenuated (APS) or frank psychotic symptoms (BLIPS) insofar as reality testing and insight into symptoms is intact (Klosterkötter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001; Frauke Schultze-Lutter, 2009).

Table 1 Ultra-high risk criteria of schizophrenia (UHR)

Attenuated positive symptoms (APS)	• Ideas of reference • Unusual thought content / magical thinking • Perceptual abnormalities • Odd thinking and speech • Paranoid ideation
Brief limited intermittent symptoms (BLIPS)	• Hallucinations • Delusions • Formal thought disorder
State-trait criterion	• Schizotypal personality disorder or familial history of psychosis • Unspecific symptoms (e.g. anxiety, depression) • Reduction in global assessment of functioning of >30% in the past year

Table 2 High-risk criterion (HR)

Cognitive-perceptive symptoms (COPER)	• Thought perseveration • Decreased ability to discriminate between ideas and true memories • Derealisation • Visual perception disturbances • Acoustic perception disturbances
Cognitive disturbances (COGDIS)	• Inability to divide attention • Disturbance of expressive speech • Disturbance of abstract thinking • Captivation of attention by details
COPER and COGDIS	• Thought interference • Thought pressure • Disturbance of receptive speech • Unstable ideas of reference

Additional to the aforementioned core symptoms, individuals meeting the risk criteria for psychosis commonly also experience negative symptoms, such as diminished emotional expression and experience, decreased ideational richness, social isolation and withdrawal, akin to that seen in schizophrenia, as well as widespread cognitive deficits, in particular in the verbal fluency, executive functions, and memory domains (Demjaha, Valmaggia, Stahl, Byrne, & McGuire, 2012, for a review consider Fusar-Poli, Deste, et al., 2012; Lin, Nelson, & Yung, 2012). The assumed natural history of illness according to the aforementioned criteria is illustrated in Fig. 1. Typically, individuals at-risk firstly experience unspecific deficits, followed by basic symptoms (HR-criteria) and subsequently by APS and BLIPS, which may ultimately lead to a clinically relevant full expression of psychosis (Fusar-Poli et al., 2013).

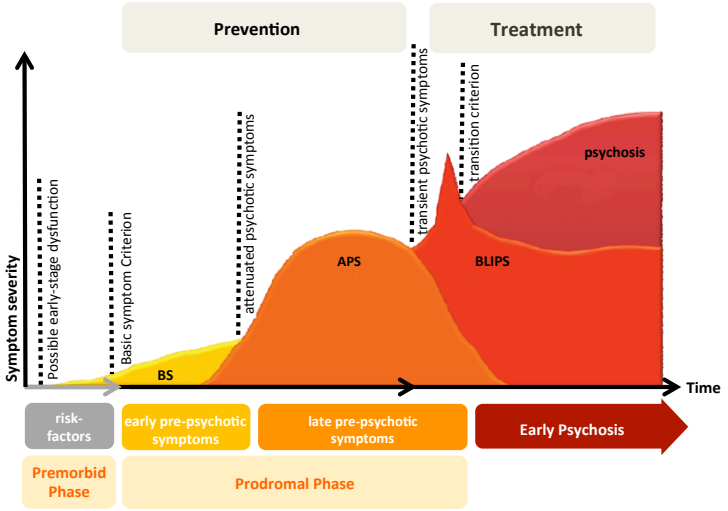

Fig. 1 Model of progression of premorbid symptoms during high-risk state to overt psychosis. The higher the line on the y-axis the higher the symptom severity. Abbreviations: BS, basic symptoms; APS, attenuated positive symptoms; BLIPS, brief limited intermittent symptoms (adapted from Fusar-Poli, 2013*).

A substantial proportion of individuals at-risk for psychosis will develop a psychotic disorder over time. However, conversion rates from prodromal states to a clinically significant psychosis range between 5-55%, depending on the diagnostic approach and follow-up period, but also on the type of analysis (Fusar-Poli, Bonoldi, et al., 2012; Gale, Glue, & Gallagher, 2013; Simon et al., 2011). Accordingly, the key

*Note: From "The psychosis high-risk state: a comprehensive state-of-the-art review" Fusar-Poli et al., 2013, JAMA, 70, p. 110. Copyright 2013 by American Medical Association. Adapted and reprinted with permission.

question is to differentiate persons who will later develop psychosis from persons who will not. Neuroimaging is a powerful tool that may enhance the specificity and validity of an early diagnosis in order to increase the predictive power for conversion to psychosis (Fusar-Poli, McGuire, & Borgwardt, 2012). Indeed, many neuroimaging studies (i. e. Smieskova et al., 2010; Wood et al., 2008) in individuals at-risk for psychosis have reported alterations in several brain regions that correspond to structural abnormalities found in schizophrenia, particularly in the prefrontal and medial temporal cortices, insula, anterior cingulate cortex (ACC) and cerebellum.

However, the transition rates implicate that most of those persons meeting the risk criteria actually will *not* develop a psychotic disorder. Nevertheless, it was demonstrated that up to 89% of adolescents with any attenuated psychotic symptom reported severe distress caused by those symptoms (Kelleher et al., 2012) and also significant suicidality has been observed in those being at-risk (Hutton, Bowe, Parker, & Ford, 2011). Moreover, non-converting individuals remained, on average, at a low level of functioning (J. Addington et al., 2011) and the clinical at-risk symptoms are persistent for a significant proportion of this population and only a minority will fully remit from these symptoms (Lin et al., 2011; Nelson et al., 2013).

Early intervention is of high importance, as it may ameliorate the course of disease or even prevent later psychosis, but ultimately it should mitigate the present symptoms. This substantiates a strong rationale of intense research in order to improve the capacity to identify those at risk for psychotic disorders and in turn enable timely interventions.

1.3. Aberrant salience processing at the dawn of psychosis

A highly salient stimulus might be a loud bang or a flash of light. However, stimulus-driven processing interacts with internal factors such as goals and beliefs. Fusar-Poli (2013) provides a revealing analogy for salience processing by describing the behavior of a hungry mouse that will mostly ignore everything that is not the smell, sight, or sound of food until an unexpected novel and potentially dangerous (salient) event, such as the shadow of a bird of prey overhead, rightly intrudes on its attention.

A crucial observation is that patients with diagnosed schizophrenia tend to over-attribute importance or significance to trivial everyday events, which leads to the formulation of the salience hypothesis of psychotic disorders. According to Kapur's (2003) seminal theory, psychotic symptoms may emerge from aberrant assignment of salience to innocuous stimuli. This is followed by top-down cognitive explanations attributed to the experiences of aberrant salience (see Poletti & Sambataro, 2013 for a review). Importantly, the phenomenon of aberrant salience processing might play a prominent role in the prodromal stage of psychosis, when individuals develop APS such as delusional ideas (see section 1.2) or, according to Jasper[3] feel that "objects, persons, and events are simply eerie, horrifying… or... mystifying, transcendental ... something must be going on; the world is changing, a new era is starting... The dog scratches oddly at the door" (cited after Mishara & Fusar-Poli, 2013, p.282).

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[3] Karl Theodor Jaspers (1883-1969); German psychiatrist and philosopher. Jaspers phenomenological approach suggests that delusion is formed through loss of context in its experiential–perceptual origins. He also identified two stages in the formation of delusions; first the rise of "delusional atmosphere", second is the patient's "working through" those experiences, sometimes "calling for the full strength of an intelligent personality", which lead to delusional ideas (Maj, 2013; Mishara & Fusar-Poli, 2013).

As mentioned earlier, two concepts are differentiated within the salience hypothesis: firstly, motivational salience corresponding to Kapurs concept (Kapur et al., 2005) and secondly, a recently proposed concept of proximal salience (Lena Palaniyappan & Liddle, 2012). Motivational salience refers to a mental process by which an external stimulus comes to awareness and drives the goal-directed behavior due to its association with reward or punishment (Tost et al., 2010) (i.e. our mouse spotting the shadow of the bird). In contrast, Palaniyappan and Liddle (2012) proposed the concept of proximal salience, in which any stimulus that is conspicuous due to incentive valence, behavioral relevance or expectancy violation (i.e. the mouse senses a bitter taste or a puff of air) would lead to a momentary state of neuronal readiness. Thus, motivational salience represents stimulus-reinforcement (action-outcome) associations, whereas proximal salience explains a more fundamental step in information processing, the stimulus-response association. In a very basic sense, this touches upon the distinction between classical conditioning and operant conditioning.

Functional magnetic resonance imaging studies revealed a crucial role for the right anterior insula (rAI) in the formation of proximal salience processing, evidenced by its central role for bottom-up processing, assisting target brain regions in generating appropriate behavioral responses to salient stimuli (Menon & Uddin, 2010). Accordingly, functional deficits mediated by the rAI may lead to excessive salience attribution to internal experiences, which consequently may be responsible for delusions and hallucinations in schizophrenia (Bressler & Menon, 2010; Menon, 2011; Palaniyappan, Mallikarjun, Joseph, White, & Liddle, 2011; Palaniyappan & Liddle, 2012). Interestingly, a well-replicated finding is that the insula was identified as being structurally altered prior to psychosis onset (Fusar-Poli, Radua, McGuire, & Borgwardt, 2012; Smieskova et al., 2012).

As mentioned above, the excess subcortical dopamine plays an important role in the pathophysiology of psychotic disorders. But how does a disturbance of the dopamine system lead to psychotic symptoms such as perceptual abnormalities and delusional ideas?

One role for dopaminergic mediated neural activity is the processing of incentive properties of a stimulus (Berridge & Robinson, 1998; Flagel et al., 2011). Indeed, there is evidence that motivation and reward processing as well as the associated cortico-striatal interactions are disturbed in schizophrenia (Heinz & Schlagenhauf, 2010; Simon et al., 2010; Ziauddeen & Murray, 2010). These findings may be secondary to chaotic dopamine firing, which would lead to overattribution of motivational salience to otherwise irrelevant cues (see Heinz & Schlagenhauf, 2010 for a review). Thus, aberrant salience processing has been hypothesized as bridging the explanatory gap between what is understood about the dysregulated dopamine system in schizophrenia and what is known about the subjective experience of psychotic symptoms (see Fig. 2, and Winton-Brown et al., 2013 for a review).

Both concepts - the proximal salience hypothesis as well as reward associated motivational salience hypothesis - have been proposed to provide meaningful explanations of clinical features seen in individuals at-risk for psychosis (Palaniyappan, White, & Liddle, 2012; Winton-Brown et al., 2013).

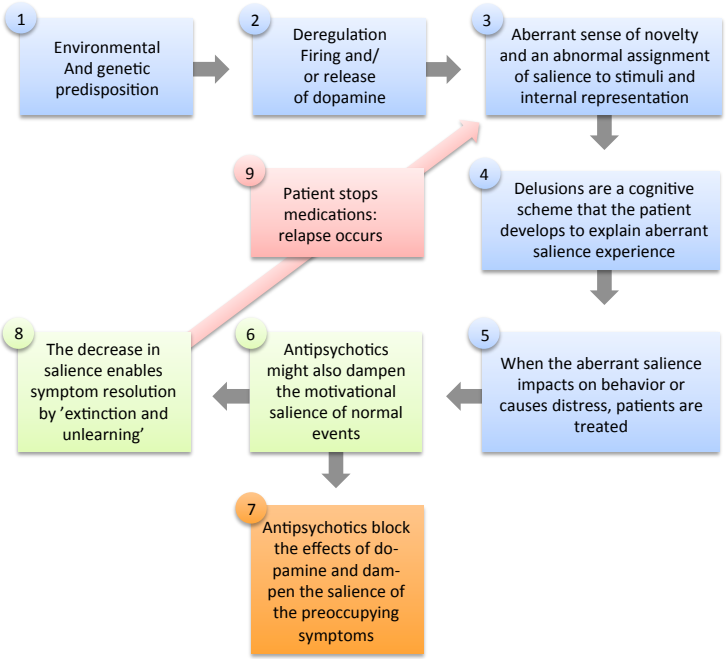

Fig. 2 The diagram shows a scheme for the chronological evolution of symptoms as a consequence of alterations in dopamine transmission and the effects of antipsychotics. The number in each box provides the relative order of the event in the sequence. Boxes 1–5 show aberrant dopamine transmission, via aberrant salience processing, leading to psychosis (adapted from Kapur, 2004)*

* *Note*: From "How antipsychotics become anti-'psychotic' – from dopamine to salience to psychosis", Kapur, 2004, TRENDS in pharmacological Sciences, 25, p. 404. Copyright 2004 by Elsevier B. V. Adapted and reprinted with permission.

1.4. Dynamics of the salience network as a linkage of aberrant proximal salience

As described in section 0, the rAI has been recognized as a central hub for proximal salience processing. Further, this region is reliably co-activated with the ACC across a variety of cognitive tasks as well as under rest, which suggests a functional network involving these regions, accordingly referred to as the *'salience network'* (Taylor, Seminowicz, & Davis, 2009). This section will elucidate the rationale of the proposed role of the salience network in processing of proximal salience.

In recent years researchers have turned their attention to investigations of how multiple brain regions interact over time. As such, functional connectivity analyses have revealed that spontaneous blood oxygen level-dependent (BOLD) signal activation is organized into spatially segregated, highly replicable functional networks (see section 2.3 and for a review see Bressler & Menon, 2010). Evidence from these studies indicates that coordinated activity of these networks might be crucial for healthy cognitive functioning (Bressler & Kelso, 2001; Buckner, Andrews-Hanna, & Schacter, 2008; Fox & Greicius, 2010; Raichle & Snyder, 2007; Uhlhaas & Singer, 2012). Importantly, disruption of these dynamics may have a decisive role in neuro-pathophysiological mechanisms of psychotic or cognitive symptoms as seen in schizophrenia (consider for a review Greicius et al., 2012).

The one network which has drawn most attention is the default mode network (DMN) that comprises a set of region involving the PCC, ventromedial prefrontal cortex, and lateral inferior parietal cortex (Fox et al., 2005; Greicius, Krasnow, Reiss, & Menon, 2003; Gusnard & Raichle, 2001). These areas are known to be co-activated during rest and importantly, deactivate during goal directed tasks, while a generic task-positive network (TPN), which includes the dorsolateral prefrontal cortex and posterior parietal cortex, is activated. Importantly, the competitive relationship between DMN and TPN is preserved under task-free conditions, which is indicated by the

anticorrelated activity between the two networks when also under rest (Fox et al., 2005; Greicius, Supekar, Menon, & Dougherty, 2009; Seeley et al., 2007; Sridharan, Levitin, & Menon, 2008). Thus, a picture emerges that DMN-TPN competition is a fundamental property of global brain function, possibly reflecting a shift between two distinct modes of information processing: the DMN, serving perceptually decoupled, inner thought in one mode, and the TPN serving focused stimulus-dependent attention in the second mode (Buckner et al., 2008; Carhart-Harris et al., 2012; Fox et al., 2005).

Crucially, during normal waking consciousness, explorative inner-thought and environmentally focused information processing do not occur simultaneously. If, however, the relationship between the DMN and TPN becomes less anticorrelated, this might reflect a confusion of states and a disturbance of cognition such as seen during drug-induced psychedelic state, which may serve as a model for psychosis (Carhart-Harris et al., 2012). Thus, a proper coordination between the DMN and TPN is considered to be of crucial importance.

Importantly, the mentioned salience network has been assigned a primary role in enabling switching between DMN and TPN. This is evidenced by a recent study using granger-causality analysis[4] of temporal dynamics in these three networks that revealed that BOLD activity in the salience network precedes and predicts activity in both the DMN and TPN (Sridharan et al., 2008). The functional connectivity maps of the three networks are depicted in the supplementary figure in section 4.6; the putative relationship between the three networks is illustrated in Fig. 3. It is hypothesized that sensory and limbic inputs are processed by the salience network. Once a salient stimulus or event is detected, the rAI initiates control signals to regulate behavior via the ACC and the homeostatic state via the mid and posterior insular

[4] A statistical method that, when applied to the brain, measures the degree of predictability of temporal changes in one brain area that can be attributed to those in another area (Goebel, Roebroeck, Kim, & Formisano, 2003).

cortex, and consequently facilitates task-related information processing by initiating appropriate transient engagement of the TPN while disengaging the DMN (Bressler & Menon, 2010; Menon, 2011). Based on these observations, Menon (2011) recently proposed a unifying triple-network model of psychopathology, in which he postulates a disruption of proper coordination of these three networks, which might lead to "aberrant saliency mapping and cognitive dysfunction in psychopathology".

The salience network is thus hypothesized not only to mediate between externally oriented attention (TPN) and internally oriented cognition (DMN), but also to initiate the recruitment of brain regions relevant for processing currently salient stimuli while decreasing activity in networks engaged in processing previously salient stimuli (Palaniyappan & Liddle 2012a).

Evidence for Menon's model has been shown in various studies in schizophrenia: Amongst others, revealing a weakening of the reciprocity between the DMN and TPN (Hasenkamp, James, Boshoven, & Duncan, 2011; Manoliu et al., 2013; Whitfield-Gabrieli & Ford, 2012), and reduced connectivity both within the salience network and *between* salience network and DMN (Pu et al., 2012; White, Joseph, Francis, & Liddle, 2010).

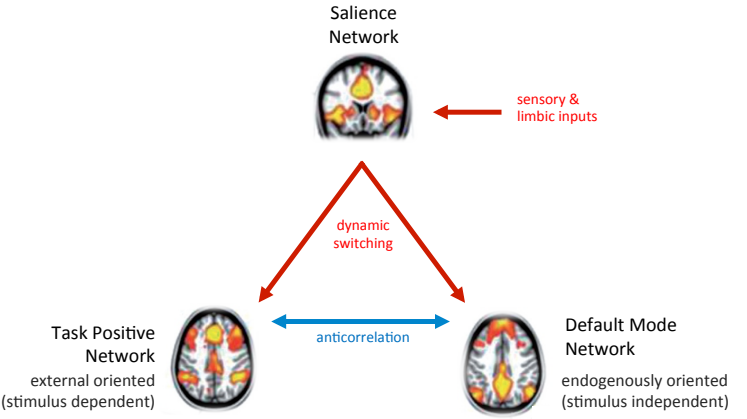

Fig. 3 According to the triple-network model, the salience network initiates dynamic switching between the task positive network and the default mode network, and mediates between attention to exogenously driven, cognitive demanding activity and endogenously mediated, self-referential mental activity. In this model, sensory and limbic inputs are processed by the salience network, which is involved in the processing of detecting salient events and initiating an appropriate control signal to regulate behavior and inner states (Bressler & Menon, 2010)*.

* *Note*: Brainimages derived from "The restless brain", Raichle, 2011, Brain Connectivity, 1, p. 3. Copyright 2011 by Mary Ann Liebert, Inc. Adapted and reprinted with permission.

1.5. Aberrant motivational salience in reward processing as a linkage of dysregulated dopamine

Goal-directed behavior is crucially linked to the pursuit of reward and the avoidance of punishment, which is thought as being decisively mediated by dopamine. FMRI studies allow the measurement of functional activation during reward processing in psychosis. However, fMRI cannot be used to directly measure abnormalities relating to the phasic increase in dopamine firing (Schultz, 2010). Nevertheless, fMRI can address hemodynamic changes, which may *result* from a dopaminergic input. Indeed, hemodynamic response within the ventral striatum (VS) in response to reward anticipation has been shown to positively correlate with dopamine release. This association was possible by obtaining fMRI measures of reward-related neural activity and positron emission tomography (PET) - measures of dopamine release in the same human participants while performing a reward based task (Schott et al., 2008; and for a review, Knutson & Gibbs, 2007).

Reward processing can be dissociated in two stages: the anticipation and the outcome of reward, which have been associated to separable neural correlates (Berridge, Robinson, & Aldridge, 2009; B Knutson, Fong, Adams, Varner, & Hommer, 2001). During feedback of reward, activity in prefrontal areas and specifically the medial orbitofrontal cortex (mOFC) reflect the hedonic experience of immediate reward responses (Kringelbach, 2005), while the VS codes for prediction error in response to unexpected rewards (Berns, McClure, Pagnoni, & Montague, 2001). Thus, as described in section 0, this stage might be associated with processing of *motivational salience*, as this process is reflecting stimulus-reinforcement associations.

During the anticipation period, in contrast, reward-indicating cues elicit additional activation in the rAI (Knutson & Greer, 2008; Krebs, Boehler, Roberts, Song, & Woldorff, 2012; Volz, Schubotz, & von

Cramon, 2004). Interestingly, the region that is speculated to be involved in the representation of proximal salience (Palaniyappan & Liddle, 2012) (see section 0).

Only recently, PET studies have suggested that dopaminergic dysregulation begins before the first psychotic episode (Howes et al., 2009; Howes et al., 2011). Particularly, the striatal dopamine synthesis capacity has been shown to increase during transition to psychosis (Howes et al., 2011). Thus, studying the reward system in the pre-psychotic stage might be promising in understanding the role of dopaminergically mediated motivational salience. Indeed, there is recent evidence for disturbed motivational salience processing and associated responses in the VS (Roiser, Howes, Chaddock, Joyce, & McGuire, 2013), as well as reduced activation of VS during loss-avoidance anticipation in pre-psychotic individuals (Juckel et al., 2012).

Chapter 2

Methods

2.1. Study Sample

Individuals were recruited within the context of a study on early recognition of psychosis (ZInEP; Zurich Program for sustainable Development of Mental Health Services, www.zinep.ch). Participants at-risk for psychosis had either learned about the study from the project website, flyers, newspaper ads, or else were referred by general practitioners, school psychologists, counseling services, psychiatrists, or psychologists.

Individuals were included into the study if they met at least one of the following criteria (see section 1.2):

- High risk state for psychosis (HR): having at least one cognitive-perceptive basic symptom or at least two cognitive disturbances as assessed by the Schizophrenia Proneness Instrument SPI-A (Adult version) (Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007) or SPI-CY (Child/Youth version)

- Ultra high risk state for psychosis (UHR): having at least one APS, or at least one BLIPS symptom as rated by the structured interview for Prodromal Syndromes, SIPS (Miller et al., 2003). Persons who met only the state-trait criteria were not included in the two studies, as the primary research interest was exploring the putative disturbances within individuals exhibiting subclinical symptoms.

Individuals for our age-, intelligence-, handedness-, and gender-matched healthy control group were recruited by advertising through webpages, flyers, university mailinglists, or through word-of-mouth. More details are given in the corresponding methods parts of the studies.

2.2. Functional magnetic resonance imaging

Neuroimaging techniques have rapidly developed into a powerful tool in psychiatric research as they provide an unprecedented opportunity for the investigation of brain structure and function (Borgwardt, 2013). FMRI provides a noninvasive measure of functional connectivity during rest and of local brain activity in response to cognitive tasks undertaken during magnetic resonance scanning; methods that will be addressed in the ensuing sections.

Exploiting neurovascular properties of neural activity, fMRI measures hemodynamic signals, which is a contrast between the magnetic susceptibility of oxygenated and deoxygenated hemoglobin, hence called the blood oxygen level-dependent (BOLD) signal (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Ogawa, Lee, Kay, & Tank, 1990). By way of explanation; when a brain region is neurally active, the supply of oxygenated hemoglobin is increased and, subsequently, the relative measure of de-oxygenated hemoglobin decreases, which results in higher signal onto T2*-weighted images[5]. Ergo, the BOLD signal can only be viewed as an indirect measure of neural activity. Additionally, while fMRI allows the reconstruction of spatially localized signals at good spatial resolution within a millimeter-scale, the slow time constants of the BOLD response result in poor temporal resolution in order of seconds (Friston, Ashburner, Kiebel, Nichols, & Penny, 2007; Jäncke, 2005; Poldrack, Mumford, & Nichols, 2011).

[5] T2* is the transverse the time constant for the decay of a magnetic resonance signal or spin-spin relaxation time in a nonhomogeneous local magnetic field.

2.3. Resting-state fMRI as a method to study functional connectivity

The human brain is a complex integrative, but highly efficient network comprising a large number of different brain regions that each have their function, but are *continuously* sharing information between structurally and functionally linked neural areas (van den Heuvel & Hulshoff Pol, 2010). Thus, different kinds of connectivity measurements can be described; structural/anatomical connections such as fiber tracts between brain regions, and functional connectivity.

Functional connectivity in the analysis of neuroimaging time-series is defined as the statistical dependencies between spatially remote neurophysiological events (Friston, Frith, Liddle, & Frackowiak, 1993). However, it is important to note that functional connectivity is simply a statement about the observed correlations. Thus, it cannot be inferred on how these correlations are mediated, and also gives no indication as to the cause, the direction or the influence of a third variable of the connection[6] (Friston, Kahan, Biswal, & Razi, 2013).

Statistical dependencies of the slow BOLD oscillations obtained from fMRI can be conducted by various methods such as seed-based and the independent component analysis (ICA) methods (Margulies et al., 2010)[7]. The applied analysis in Study I was the seed-based approach in

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[6] Though, it can be analyzed using dynamic causal modeling (Friston et al., 2013), granger causality analysis (Goebel et al., 2003) or multidimensional scaling (Ryali, Supekar, Chen, & Menon, 2011).

[7] A pellucid analogy was made by Margulies and colleagues (2010) by comparing the various methodologies in rsfMRI analysis by describing the dynamic interactions of a cocktailparty: We might choose an individual, such as the host, and describe his interactions with each of the guests (*seed-based functional connectivity*). Or we would map out the predominant lines of conversation (*ICA*) or the cliques that formed throughout the evening (*clustering*), or abstract the lines of communication (*graph theory*) or search for delineating patterns of activity (*pattern classification*). Or we might simply describe the behavior of the guests individually ("*local*" approaches).

order to identify networks of functional connectivity. Application of this method requires a selection of a priori seed-ROI (see Fig. 4(1)). Briefly, in a first step the BOLD signal times-series are extracted from the corresponding seed, which is used to search the brain for other voxels[8] whose BOLD signal fluctuations are significantly correlated (van den Heuvel & Hulshoff Pol, 2010). The pearson's correlation coefficients can then be converted to normally distributed scores using Fisher's transform to allow for second-level general linear model (GLM) analyses. The so obtained correlation maps (see Fig. 4(2)), however, depend on the specific location of the seed (Whitfield-Gabrieli & Ford, 2012). For example, typically the MPFC or PCC is used for identifying the DMN, anticorrelated to the seed then we find the regions of the TPN, the correlation maps from the rAI will result in the salience network (vide supra; section 1.4). Notably, the resulting networks using the hypothesis driven seed-based approach are comparable to those from data driven ICA approach (Rosazza, Minati, Ghielmetti, Mandelli, & Bruzzone, 2012).

Functional connectivity can be analyzed from data measured during the processing of a cognitive task, but also under rest, whilst the subjects are asked to rest quietly with their eyes closed for several minutes. There is an ongoing debate whether it is a valid method to study the human brain (i. e. "Does the brain have a baseline? Why we should be resisting a rest", Morcom & Fletcher, 2007). A maybe clarifying distinction was formulated by Raichle (2010), where he stated that the important distinction was not between rest and task, but rather between task-*evoked* and *intrinsic* activity, the former is based on the perspective that the brain is "primarily reflexive, driven by the momentary demands of the environment", while the latter posits the alternative possibility that the "brains operations are mainly intrinsic, involving the acquisition and maintenance of information for

[8] A term for a (3-dimensional) volume element.

interpreting, responding to, and even predicting environmental demands" (Raichle, 2009, p. 1279).

Despite the open questions about the nature of rsfMRI it is gaining increasing attention, particularly in attempts to characterize differences in intrinsic functional connectivity maps between different groups of subjects, i.e. a patient group to the control group. Importantly, because secondary analyses in a patient sample allow correlations to a disease measure (such as the degree of positive symptoms and the connectivity values) (Greicius, 2008).

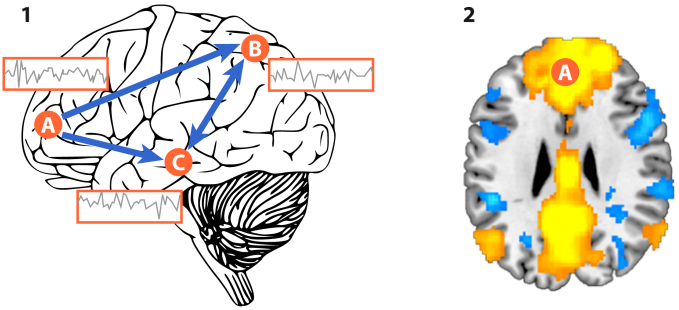


Fig. 4 The main steps in taking resting-state functional magnetic resonance imaging (rsfMRI) data for functional connectivity analysis. 1) During rsfMRI the spontaneous temporal fluctuations in brain activity is measured. Consequently, the BOLD signal time-series are extracted in previously defined seed regions (here illustrated by exemplary seeds A, B C). 2) The time-series of one seed (A, within medioprefrontal cortex) will then be used as a regressor to search the brain for correlated time series. The voxel values then reflect the degree to which a given voxel is correlated with the seed (in this case the resultant correlation map in yellow reflects the default mode network, in blue, the anticorrelated task-positive network).*

* *Note*: The pictures of time-series in 1) derived from "Functional connectomics from resting-state fMRI" by (Smith et al., 2013), Trends in cognitive sciences, 17, 12 p. 110. Copyright 2013 by Elsevier Ltd. and 2) from "Aberrant Coupling Within and Across the Default Mode, Task-Positive, and Salience Network in Subjects at Risk for Psychosis", by Wotruba et al., 2014, Schizophrenia Bulletin. Copyright 2013 by Oxford University press. Adapted and reprinted with permission.

2.4. Task-based fMRI as a method to study reward processing

FMRI can provide a measure of local brain activity in response to cognitive tasks. The aim is to infer about the role of particular brain regions in a cognitive function of interest. Thus, a stimulus is manipulated during MR-scanning, and activation maps are obtained by comparing the signals recorded during different states (such as some experimental condition vs. a control condition). In Study II, a modified variant of the monetary incentive delay task (Abler, Walter, & Erk, 2005) was used; participants first saw a cue stipulating with an unpredictable probability amount of money they could win, if they reacted correctly during an ensuing discrimination task (anticipation). Immediately after target presentation, subjects were informed about the amount of money they had won (feedback). This experiment was constructed as an *event-related design.* In such a design the events are discrete and are presented in a punctuated fashion. Further, the events occur in a randomized order at non-constant inter-trial intervals with longer periods of control condition, which allows the hemodynamic response to return to baseline, and thus maximize the ability to distinguish among their BOLD contribution. Consequently, the time-course of the hemodynamic response function (HRF) following each stimulus can be estimated. This type of designs covers important advantages: the design analyses permits high flexibility as any property could be used to define different classes of events, and as such allows measuring item-related neural processes. On the other hand, a long length of the experiment is often necessary to obtain a sufficient statistical power.

Within a general linear model (GLM) approach the correct linear combination of explanatory variables are attempted (e.g., hemodynamic response due to a subject's task performance, confounding effects due to motion, respiratory and cardiac dynamics) that account for the temporal response observed at each voxel during an experiment. The specific effects are then tested by contrasting

between different experimental conditions, i.e. reward anticipation vs. no reward anticipation in our case. This contrast will then display the neuronal network involved in reward anticipation. To make inferences on group level, the individual contrast images are then subjected to a random effect analysis (in our case), to permit population-level inferences or a fixed effects approach.

Importantly, a typical fMRI data set can contain a few tens of thousands of voxels. Thus, using a conventional threshold (e.g., *alpha* of 0.05) will result in an enormous number of type I errors (false positives). Conversely, the use of very strict correction factors (e.g. Bonferroni comparison) risks missing many regions with true activity (e.g., type II errors). A common compromise between these extremes is the use of gaussian random field theory, a nonexclusive approach, that is to require clusters of activation to reach a particular size (i.e. estimated by means of the so-called monte carlo simulation) to be counted as significant. Another method is the restriction of voxel-wise analyses to a set of regions of interest (ROIs) and then controlling for multiple comparisons only in those voxels, while in order to circumvent double-dipping the ROIs need to be independent of the data being analyzed (i.e. from anatomical atlases or from independent data, based on previous studies) (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009; Poldrack, 2007; the description of methods are based on Friston et al., 2007; Jäncke, 2005, Poldrack et al., 2011).

Chapter 3

Aims and research questions

The primary aim of this PhD project was to assess salience associated processing in the brain of individuals at risk for psychosis in order to provide further insight into illness susceptibility, and consequently the neuropathophysiological mechanisms of psychotic disorders.

The motivation for this main aim is based on previous research investigating the putative aberrant salience processing in schizophrenia. These previous studies provided major insights about neuronal mechanisms of salience processing, revealing two concepts being promising to study: first, *proximal salience* and second, *motivational salience*. Considering that proximal salience may be studied indirectly via functional connectivity analysis of the salience network, and motivational salience via reward-based processing, the review of the pertinent research literature emerged in the following research gaps:

First, increased TPN–DMN coupling has been found in individuals at ultra-high risk for psychosis (Shim et al., 2010). However, neither Menons triple-network theory of psychopathology has been tested in the pre-psychotic period so far, nor if the salience network and its functional connectivity to the DMN and TPN were associated to symptoms related reality distortions and cognitive processing. Further, it is assumed that HR and UHR criteria mirror complementary clinical features (HR the self-perceived cognitive and perceptual change clearly distinguishable from subthreshold psychotic symptoms included in UHR criteria). Additionally, the former characterizes the early prodromal phase, the latter the late prodromal stage. However, it was not yet tested, if intrinsic functional connectivity differs between those two clinical stages.

Second, previous studies exploring reward related processing included schizophrenic patients treated with antipsychotic and/or sedative medications. Thus it is uncertain, if the findings of aberrant reward processing predate or are secondary to the development of psychosis, and additionally, whether medication confounded the findings (particularly supposing that antipsychotics block dopamine

transmission and thereby may induce blunting of the brain reward system sensitivity). There is recent evidence for perturbed motivational salience processing to neutral stimuli (Roiser et al., 2013), as well as reduced striatal activation during loss-avoidance anticipation in medicated prepsychotic individuals (Juckel et al., 2012). However, the brain correlates of both, anticipation and feedback of reward and its association to symptoms associated to reality distortions, depressive and negative symptoms in subjects at risk for psychosis has not yet been studied.

This dissertation, which aligned a cross-sectional study design comparing healthy control subjects with persons at risk for developing psychosis, and used resting-state and task-based fMRI methods, included two studies. The first study focused on proximal salience by studying it indirectly through the analysis of intrinsic functional connectivity within and between the salience network, DMN, and TPN, whereas the second study focused mainly on motivational salience processing by employing a modified version of the monetary incentive delay task that allows investigating the neural response to reward expectation and reward outcomes.

Chapter 4

Study I: Aberrant coupling within and across the default-mode, task positive, and salience network in subjects at risk for psychosis

4.1. Abstract

The task-positive network (TPN) is anticorrelated with activity in the default-mode network (DMN), and possibly reflects competition between the processing of external and internal information, while the salience network (SN) is pivotal in regulating TPN and DMN activity.

Because abnormal functional connectivity in these networks has been related to schizophrenia, we tested whether alterations are also evident in subjects at risk for psychosis. Resting-state functional magnetic resonance imaging was tested in 28 subjects with basic symptoms reporting subjective cognitive-perceptive symptoms; 19 with attenuated or brief, limited psychotic symptoms; and 29 matched healthy controls. We characterized spatial differences in connectivity patterns, as well as inter-network connectivity. Right anterior insula (rAI) was selected as seed region for identifying the SN; medioprefrontal cortex (MPFC) for the DMN and TPN.

The three groups differed in connectivity patterns between the MPFC and right dorsolateral prefrontal cortex (rDLPFC), and between the rAI and posterior cingulate cortex (PCC). In particular, the typically observed antagonistic relationship in MPFC–rDLPFC, rAI–PCC, and inter-network connectivity of DMN–TPN was absent in both at-risk groups. Notably, those connectivity patterns were associated with symptoms related to reality distortions, whereas enhanced connectivity strengths of MPFC–rDLPFC and TPN–DMN was related to poor performance in cognitive functions.

We propose that the loss of a TPN–DMN anticorrelation, accompanied by an aberrant spatial extent in the DMN, TPN, and SN in the psychosis-risk state, reflects the confusion of internally and externally focused states and disturbance of cognition, as seen in psychotic disorders.

4.2. Introduction

Resting-state functional magnetic resonance imaging (rs-fMRI) has revealed that spontaneous blood oxygen level-dependent (BOLD) signal activation is organized into spatially segregated functional networks (Damoiseaux et al., 2006; Fox et al., 2005; Gusnard & Raichle, 2001; Raichle et al., 2001). Rs-fMRI studies applying intrinsic functional connectivity (iFC) analysis have shown that coordinated activity of dynamically configured large-scale brain networks is crucial for cognitive and executive functions (Bressler & Kelso, 2001; Buckner et al., 2008; Fox & Greicius, 2010; Raichle & Snyder, 2007; Uhlhaas & Singer, 2012). Disruption of these dynamics possibly leads to various pathological states, such as psychotic or cognitive symptoms as seen in schizophrenia (Broyd et al., 2009; Fox & Greicius, 2010; Greicius, 2008). Indeed, these iFC abnormalities may play an important role in the pathogenesis of psychotic disorders. Particularly, research has focused on disturbances of the default-mode network (DMN), the task-positive network (TPN), and the salience network (SN) (Bluhm et al., 2007; Chai et al., 2011; Garrity et al., 2007; White et al., 2010; Whitfield-Gabrieli & Ford, 2012; Williamson, 2007; Woodward, Rogers, & Heckers, 2011). The DMN, also known as the task-negative network, involves the posterior cingulate cortex (PCC), the medial prefrontal cortex (MPFC), and the lateral inferior parietal cortex. Activity in those regions is greater in individuals at rest than when engaged in goal-directed tasks and, correspondingly, has been associated with internally guided, perceptually decoupled thoughts, such as mental simulation or episodic retrieval (Anticevic et al., 2012; Fox et al., 2005; Greicius et al., 2003; Gusnard & Raichle, 2001; Mason et al., 2007; Smallwood et al., 2013; Whitfield-Gabrieli et al., 2011). The DMN is anticorrelated with activity in the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex that form the TPN (also referred to as central-executive network), a set of regions induced during goal-oriented activity (Fox et al., 2005; Greicius et al., 2009; Seeley et al., 2007; Sridharan et al., 2008).

This suggests that the DMN–TPN antagonistic relationship is a fundamental property of the brain, possibly reflecting a shift between two distinct modes of information processing: the DMN, serving untargeted inner thought in one mode, and the TPN, serving focused, one stimulus-dependent attention in the second mode (Buckner et al., 2008; Carhart-Harris et al., 2012; Fox et al., 2005).

Evidence is also increasing that the functional competition between DMN and TPN is regulated by SN, which comprises the right anterior insula (rAI), ventrolateral prefrontal cortex, and anterior cingulate cortex (Deshpande, Santhanam, & Hu, 2011; Seeley et al., 2007; Sridharan et al., 2008). The rAI has a central role for bottom-up processing, assisting target brain regions in generating appropriate behavioral responses to salient stimuli (Menon & Uddin, 2010). Moreover, the rAI is involved in the representation of current and predictive salience, particularly in the context of interoception (Palaniyappan & Liddle, 2012).

In schizophrenia, anomalies can occur in the coordination between DMN and TPN (Chai et al., 2011; Shen, Wang, Liu, & Hu, 2010; Whitfield-Gabrieli et al., 2009), at times weakening the reciprocity between those networks (Hasenkamp et al., 2011; Manoliu et al., 2013; Whitfield-Gabrieli & Ford, 2012). Individuals with schizophrenia have reduced connectivity both within SN and between SN and DMN (Pu et al., 2012; White et al., 2010). Dynamic suppression of DMN is generally associated with better performance of attention-demanding tasks (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). Hence, the DMN hyperconnectivity, as seen in schizophrenia, may be related to impairments in attention and working memory and overly intensive self-referential and introspective processing (van Buuren, Vink, & Kahn, 2012; Whitfield-Gabrieli & Ford, 2012). Emerging evidence has attributed those cognitive deficits in schizophrenia to dysfunctions in proper DMN–TPN coordination whereas SN anomalies have been associated with reality distortion (Palaniyappan & Liddle, 2012; Pu et al., 2012).

Early in their prodromal phase of illness, most schizophrenia patients already exhibit attenuated or brief, limited psychotic symptoms and subtle, self-experienced disturbances in perception, thoughts, and cognition (Addington & Heinssen, 2012; Andreasen et al., 2010; Salokangas & McGlashan, 2008). Considering the changes in connectivity observed in schizophrenia, examining iFC in individuals at increased risk of developing psychosis may provide further insight into illness susceptibility and its underlying neuropathophysiological mechanisms. A reduced iFC between Broca's area and the lateral and medial frontal cortices (Jung et al., 2012), plus increased TPN–DMN coupling, have been found in individuals at ultra-high risk for psychosis (Shim et al., 2010). However, whether the risk-state for psychosis is additionally associated with SN disturbances has not yet been investigated. Furthermore, to our knowledge this is the first study exploring both, within- and between iFC, and its association to symptoms related to reality distortions and cognitive processing in subjects at risk for psychosis.

Based on these previous findings, we hypothesized that clinical symptoms and disturbances of cognition seen in at-risk subjects are reflected by an aberrant spatial extent in DMN, TPN and SN, accompanied by a loss of anticorrelation between those three networks. To test this, we evaluated rs-fMRI in three groups of subjects: 28 at risk for psychosis with basic symptoms (high-risk criteria, HR), who described subtle, often only self-perceivable deficits (Klosterkötter et al., 2001); 19 with attenuated and/or brief, limited intermittent psychotic (positive) symptoms (Yung & McGorry, 2007) (ultra-high-risk criteria, UHR); and 29 healthy controls (CTRL). With this group separation, we also investigated whether iFC differs in the two clinical stages of risk because it is presumed that HR criteria characterize the early prodromal phase whereas UHR reflects the late prodromal phase (Fusar-Poli et al., 2013; Klosterkötter et al., 2011). Using a seed-based approach, we first examined iFC to identify variations in spatio-temporal connectivity in SN, DMN, and the TPN among the three groups. We then tested group differences in inter-network connectivity

via Pearson's correlations between the first eigenvariate of each network. Finally, we explored possible relationships among significant aberrant iFC strength with severity of clinical symptoms, and cognitive variables.

4.3. Methods

Participants

This study consisted of 76 participants (29 CTRL, 28 HR, and 19 UHR) and was approved by the local ethics committee of Zurich. The risk groups were recruited in the Swiss region of Zurich within the context of a larger study on early recognition of psychosis (www.zinep.ch, last accessed: Oct. 29th, 2013). Following an initial screening, in-person diagnostic interviews were administered. After the subjects received complete project descriptions, we obtained their written, informed consent.

Participants reporting at least one cognitive-perceptive basic symptom or at least two cognitive disturbances, as assessed by the adult version of the Schizophrenia Proneness Interview (SPI-A), fulfilled the inclusion criterion for the HR status for psychosis (Schultze-Lutter et al., 2007). Those describing at least one attenuated psychotic symptom or brief, limited, intermittent psychotic symptom, as assessed by the Structured Interview for Prodromal Syndromes (SIPS), fulfilled the criterion for UHR status (Miller et al., 2003). Four HR subjects and six in the UHR cohort were taking second-generation (atypical) antipsychotic medication at the time of scanning. Chlorpromazine (CPZ)-equivalents were calculated for them (Andreasen et al., 2010). Five subjects each in the HR and UHR groups were being treated with an antidepressant.

Our healthy CTRLs were recruited through advertisement. Screening with the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) was conducted to ensure that none had any current or prior

history of psychiatric illness. Those receiving any medications were excluded.

Persons in HR, UHR, and CTRL were matched for handedness, sex, age, and IQ (Table 1). The groups had a mean of estimated premorbid intelligence slightly above average, as assessed using a German test for fluid, nonverbal intelligence (LPS-3) (Horn, 1983). Handedness was examined by the Edinburgh Handedness Inventory (Oldfield, 1971). Exclusion criteria were contraindications against MRI, pregnancy, history of neurological illness, drug-, or alcohol dependence. Structural MRI scans were neurologically screened by an experienced neuroradiologist, and participants with structural brain abnormalities such as hyperintensities on Fluid Attenuated Inversion Recovery (FLAIR) sequences and other incidental lesions were excluded.

Imaging data acquisition

Rs-fMRI data were acquired at the Zurich University Hospital of Psychiatry, Switzerland, using a Philips Achieva TX 3-T whole-body MR unit with an eight-channel head coil. Functional scans (6-min runs) involved a sensitivity-encoded single-shot echo-planar (factor 1) T2*-weighted echoplanar imaging sequence (EPI) [repetition time (TR)=2000 ms; echo time (TE)=35 ms; field of view (FOV)=220x220 mm^2; acquisition matrix=88x87, interpolated to 128x128; 32 contiguous slices with a spatial resolution of 2.5x2.5x4 mm^3 (reconstructed 1.72x1.72x4 mm^3); flip angle θ=78°; and sensitivity-encoded acceleration factor R=1.8]. Using a mid-sagittal scout image, we placed the contiguous axial slices along the anterior-posterior commissural plane, which covered the entire brain, and were acquired in ascending order. We also acquired three-dimensional T1-weighted anatomical images [160 slices; TR=1900 ms; TE=2.2 ms; inversion time=900 ms; θ=78°; spatial resolution, 1x1x1 mm^3 (reconstructed 0.94x0.94x1 mm^3); FOV=240x240 mm^2]. The EPI sequences were conducted in darkness and participants were asked to keep their eyes closed during the session, lie as quietly as possible, and avoid falling asleep. Accuracy of compliance to these instructions was controlled by verbal confirmation

immediately after the scan sequence. To minimize potential arousal and anxiety effects, we started rs-fMRI data acquisition 10 min after subjects were moved to their final positioning in the MR bore.

Table 1 Demographic characteristics and symptom rating

	CTRL	HR	UHR	Statistical Evaluation
N	29	28	19	
Gender (f:m)	13:16	13:15	6:13	χ^2=1.17, *n. s.*[a]
Handedness(r:l:b)	25:2:2	25:1:2	18:1:0	χ^2=1.71, *n. s.*[a]
Age (years)	22.8 ± 5.0	24.01 ± 5.6	20.3 ± 3.9	*F*=3.1, *n. s.*[b]
Estimated intelligence (LPS-3)	119.82 ± 8.5	113.33 ± 2.7	117.05 ±2.1	*F*=1.4, *n. s.*[b]
SIPS:				
- Positive	-	4.32 ± 2.52	10.11 ± 3.31	*U*=45.00, *p*<.000[c]
- Negative	-	8.75 ± 5.58	12.37 ± 6.28	*U*=164.00, *p*=.03[c]
- General	-	6.61 ± 3.38	7.47 ± 3.76	*U*=215.00, *n. s.*[c]
- Disorganization	-	2.61 ± 1.50	5.30 ± 2.34	*U*=86.50, *p*<.000[c]
GAF	-	64.04 ± 13.6	59.1 ± 11.26	*U*=1.27, *n. s.*[c]
CPZ equivalents	-	5.1 ± 14.1	128.2 ± 380.3	*U*=208.5, *n. s.*[c]

Abbreviations: CTRL, healthy controls; HR, subjects at risk for psychosis; UHR, subjects at ultra-high risk for psychosis; SIPS, symptoms according to Structured Interview for Prodromal Syndromes; GAF, Global Assessment of Functioning Scale Mean; CPZ equivalents, Chlorpromazin equivalents; r:l:b, r=right l=left b=both/bimanual. [a]Pearson's chi-square test; [b]three-level analysis of variance test; [c]Mann-Whitney U-test; *n.s.*, not significant (*p*>.05). ±SD where appropriate.

Data analysis

Post-processing of the rs-fMRI data was conducted using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm, last accessed: Oct. 29th, 2013), running in Matlab (Mathworks Inc., Sherbon, MA, USA). The steps included realignment, slice timing correction, coregistration to structural T1 scan, spatial normalization to Montreal Neurological Institute coordinates (MNI), and spatial smoothing (8 mm Gaussian kernel). The structural scans were segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) tissue classes, per the unified segmentation approach (Ashburner & Friston, 2005). Using the SPM8 default values, the number of Gaussians were two for each; GM, WM, CSF, and four for everything else. None of the participants had to be excluded due to excessive head motion (linear shift <2 mm across and, on a frame-to-frame basis, rotation <1°). Head motions in any direction did not differ significantly among the three groups (3-level ANOVA; all F <1.6, p>0.14).

The CONN-fMRI functional connectivity toolbox v13 (http://www.nitrc.org/projects/conn, last accessed: Oct. 29th, 2013) was used to apply bandpass filtering (0.008 Hz < f < 0.09 Hz) and to create individual seed-to-voxel connectivity maps (Whitfield-Gabrieli & Nieto-Castanon, 2012). Spurious sources of noise, such as heart rate and respiration signals, were first estimated by the anatomical component base noise reduction strategy (aCompCor) (Behzadi, Restom, Liau, & Liu, 2007), and then included with the head-movement parameters as nuisance regressors in a general linear model. The aCompCor algorithm efficiently removes principal components from WM and CSF regions, and therefore does not rely on global signal regression, which can artificially introduce negative correlations (Chai, Castañón, Ongür, & Whitfield-Gabrieli, 2012; Murphy, Birn, Handwerker, Jones, & Bandettini, 2009). Based on experimental data from a schizophrenic population (Gabrieli et al., 2009; Garrity et al., 2007; Hasenkamp et al., 2011; Manoliu et al., 2013) and recently proposed theoretical models for disturbance in the triple

network (Menon, 2011), we tested spatio-temporal differences in interactions within and across DMN, TPN, and SN. To compare our results with existing iFC findings, we centered two *a priori*-determined seed regions of interest (ROI) on MNI coordinates, based on previous studies (Chai et al., 2011; Fox et al., 2005; Seeley et al., 2007; Whitfield-Gabrieli et al., 2009; Woodward et al., 2011). The SN consisted of the correlation with the rAI (MNI coordinates: x=38 y=22 z=–10). In accordance with results reported by Fox et al. (Fox et al., 2005) and Fransson et al. (Fransson, 2005), we defined DMN by regions showing positive correlations with the MPFC seed (MNI coordinates: x=–1 y=49 z=–2); the TPN was then defined by regions showing negative correlations with that seed. The seed-ROIs of 8-mm-radius spheres were created with the MARSBAR toolbox (http://marsbar.sourceforge.net/, last accessed: Oct. 29th, 2013). Intrinsic connectivity networks were estimated on the basis of fMRI time-series, and a bivariate Pearson's correlation analysis was performed between the seed-ROIs ascribed above and all other voxels in the brain. Cortical surface projection was performed for visualization using the (PALS)-B12 atlas (Van Essen, 2005) and Caret software (Van Essen et al., 2001).

To test for spatial differences among HR, UHR, and CTRL groups in each network, we entered the connectivity maps from all participants into a 3-level ANOVA to identify regions with different iFC among groups. Regions from the ANOVA that survived a voxel-level height threshold of $p<0.001$ and an familywise error rate (FWE)-corrected cluster-level extent threshold of $p<0.05$ subsequently served as ROIs for *post-hoc* analysis. Fisher *z*-transformed Pearson correlation values were used to compute the strength of iFC between either the MPFC- or rAI seed and each ROI, and to examine the directionality of connectivity for each group.

We then aimed to determine whether, in addition to spatial differences *within* the networks, also the inter-network coupling varied among groups by assessing the inter-network connectivity of DMN–TPN, DMN–SN, and TPN–SN. To test whether connectivity differences are

not only driven by an aberrant spatial extent of the networks, we conducted the analysis by using the same connectivity maps for all three groups. To estimate the extent to which between-network coupling differed from the normal inter-network coupling, we followed similar analysis of former studies (Chai et al., 2011; Gabrieli et al., 2009; Woodward et al., 2011) and extracted the networks from our healthy control-group. Visual inspection of the networks indicated that the connectivity maps were consistent with prior findings (f.e. Sridharan et al., 2008) (see Fig. 2 A and S1). For the DMN, a single mask of within group thresholded map (whole-brain cluster corrected *alpha* .05 for voxel-wise *p*-value of .001) was created, containing voxels that positively correlated with the MPFC-seed ROI; for the TPN containing voxels that negatively correlated with the same ROI. Similarly, a single mask for the SN contained voxels that positively correlated with the rAI. We then calculated the first component from a single-value decomposition of the non-central second moment of the BOLD timeseries within each mask. These components correspond to the first eigenvariate, which is a summary of the responses within a ROI and, unlike the average, does not assume homogenous responses within a ROI (Friston, Rotshtein, Geng, Sterzer, & Henson, 2006). These were extracted for each subject. To calculate coupling strengths, we performed pair-wise Pearson's correlations between each first eigenvariate of the rs-fMRI time-series within each network. Those z-transformed correlation values were then entered into a 3-level ANOVA ($p<0.05$, corrected for multiple comparisons) to examine putative differences among groups. In correspondence to the analysis described above, first we aimed to identify the main-effect of significant group-differences by a 3-level ANOVA. Subsequently, *post-hoc* we performed an unpaired 2-sample *t*-test, to learn which group drives the effect. As a subsidiary analysis, we computed one-sample *t*-test of the Fisher *z*-transformed Pearson correlation values, which served as an index of coupling strength for each group.

The z-values of aberrant iFC were used to determine how iFC strength and severity of clinical symptoms were related in at-risk subjects. As

the HR- and UHR groups were selected based on criteria that were also used to calculate the correlations, we avoided reporting any significance values and thus took account of the issue of circular analysis (Kriegeskorte et al., 2009). Spearman's correlation analysis was performed to test for relationships between altered iFCs of the rAI–PCC, MPFC–rDLPFC, DMN–TPN, and clinical symptom sum-scores, as assessed by the SIPS and SPI-A clinical interviews. Additional Pearson correlations were examined between altered iFCs and cognitive domains known to be associated with early psychotic symptoms, we report the Bonferroni corrected significance level at *alpha*<0,003. Selective attention was measured using the Frankfurter Aufmerksamkeits-Inventar (FAIR) (Moosburger & Oelschlägel, 1996). Executive function was assessed by the Rey-Osterrieth Complex Figure Test (ROCF) (Osterrieth, 1944; Rey, 1941) and the computer-administered Tower of Hanoi (TOH) (Gediga & Schöttke, 2006), using age-standardized *z*-scores. The normality of the score distributions was verified by the Kolmogorov-Smirnov-test.

4.4. Results

Seed-based analysis

In order to explore differences in spatial extent, i.e. to identify regions with aberrant iFC to the seeds, the connectivity maps from all participants were entered into a 3-level-ANOVA. Our results showed that, among subject groups, differences were significant between the iFC of the MPFC seed and a single cluster in the right DLPFC (rDLPFC) (Brodmann Area (BA) 9/46, MNI peak coordinates: x=56 y=26 z=28, cluster size=222 voxels). For the SN, differences were significant between the rAI seed and bilateral PCC (BA31/23, MNI peak coordinates: x=6 y=–26 z=30, cluster size=201 voxels). The significant clusters were plotted onto areas that were anticorrelated with MPFC in CTRL, thereby revealing an overlap of DLPFC with the

so-defined TPN. Similarly, PCC was an integral part of the DMN, as shown by areas with positive correlation to the MPFC (Fig. 1 A1, B1).

Aberrant coupling between the seeds and corresponding clusters in HR and UHR groups compared with CTRL was manifested by post hoc ROI-level t-tests (Fig. 1 A2, B2). CTRL showed a significant anticorrelation between the MPFC and rDLPFC connectivity (mean z=–0.14, t=–5.5, p<0.0001, Cohen's d=1.08). By contrast, HR, but not UHR, had a positive coupling (mean z=0.08, t=3.0, p<0.005, Cohen's d=0.53) (see also Fig. S3. Furthermore, CTRL had a significant inverse coupling between rAI and PCC (mean z=–0.05, t=–2.1, p<0.05, Cohen's d=0.33), while the rAI seed was positively coupled with the PCC in both HR (mean z=0.09, t=3.8, p<0.0005, Cohen's d=0.69) and UHR (mean z=0.15, t=5.2, p<0.0001, Cohen's d=1.5) (see also Fig. S3). Whereas HR and UHR showed no significant differences in MPFC–rDLPFC connectivity (p=0.56), the difference regarding rAI and PCC connectivity trended toward significance (p=0.09).

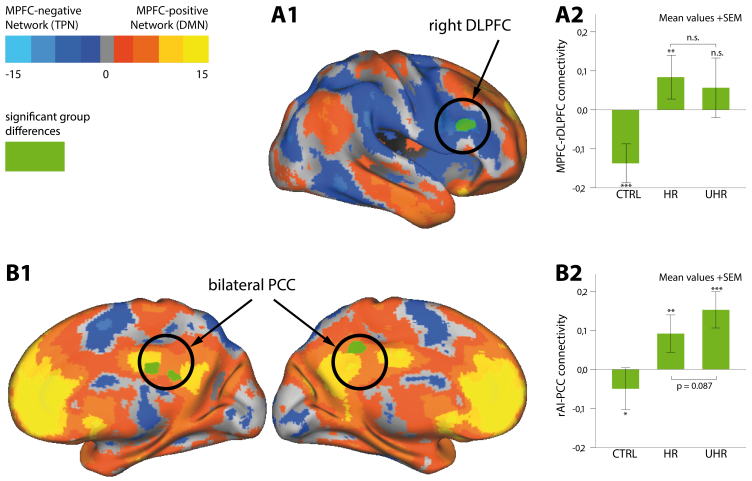


Fig. 1 Spatial differences in intrinsic functional connectivity (iFC) networks among healthy controls (CTRL), subjects at high risk (HR), and ultra-HR for psychosis (UHR). Three-level ANOVA revealed significant differences (in green) in iFC between medioprefrontal cortex (MPFC) seed and right dorsolateral prefrontal cortex (rDLPFC) (A1), and between right anterior insular (rAI) cortex seed and posterior cingulate cortex (PCC) (B1). Projection of significant clusters onto areas anticorrelated with MPFC from CTRL (blue) indicated overlaps of rDLPFC with so-defined task-positive network (TPN), as well as PCC with the default mode network (DMN), i.e., areas positively correlated with MPFC (orange). (A2) MPFC-rDLPFC was anticorrelated in CTRL, positively coupled in HR, and not coupled in UHR. (B2) CTRL revealed inverse coupling in rAI-PCC, while HR and UHR showed positive couplings with the seed. Bars represent average iFC of MPFC-rDLPFC and rAI-PCC among subjects within each group. Error bars indicate standard error of the means (SEM). ***$p < .0001$; **$p < .01$; *$p < .05$; n. s., $p > .05$.

Inter-network functional connectivity

In order to determine if connectivity differences are not only driven by an aberrant spatial extent within the networks, we assessed if the inter-network FC varied among groups. Significant group differences for inter-network connectivity were found between the DMN and TPN (F=6.3, p=0.003), and coupling in DMN–SN also trended toward significance (F=2.6, p=0.08). Significant anticorrelations were shown between the DMN and TPN in CTRL by *post-hoc* one-sample t-tests (mean z=–0.21 t=–5.2 p<0.0001 Cohen's d=0.96). In contrast, neither HR (mean z=0.04 t=–0.74, p=0.46, Cohen's d=0.14) nor UHR (mean z=0.05 t=–0.69, p=0.50, Cohen's d=0.16) exhibited significant coupling for DMN-TPN (Fig. 2 C and S4).

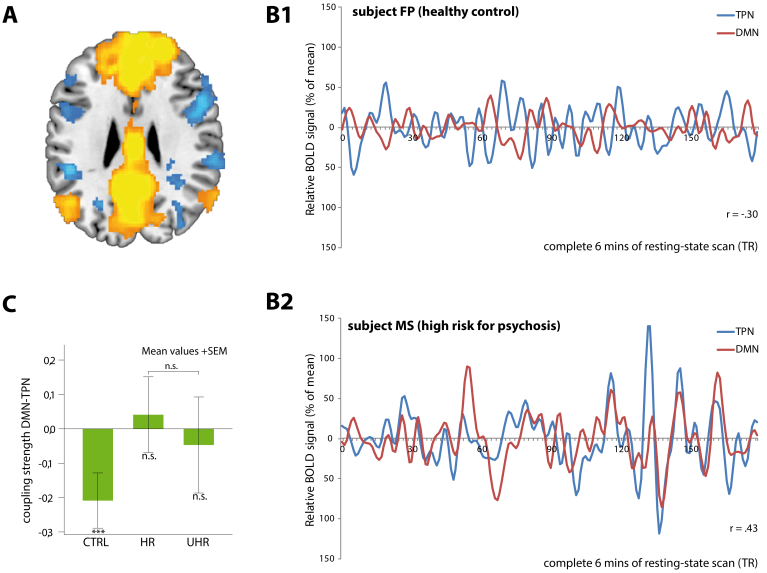


Fig. 2 Absence of anticorrelation between default mode network (DMN) and task-positive network (TPN) in subjects at risk for psychosis. (A) Seed-based functional connectivity for medioprefrontal cortex in healthy controls (CTRL) was used to derive spatial masks for DMN (yellow) and TPN (blue). Single-subject time series are illustrated for DMN (red) and TPN (blue) seen in CTRLs (B1) and persons meeting high-risk (HR) criteria (B2). Note increased TPN-DMN coupling in HR subject. (C) Group-level analysis showed no significant anticorrelations between TPN and DMN in HR and ultra-HR (UHR) compared with CTRL. Bars represent average DMN-TPN coupling among subjects within each group. Error bars indicate standard error of the means (SEM).

Correlations among functional connectivity strength, clinical symptoms, and cognitive functions

The iFC values were used to determine how iFC strength and severity of clinical symptoms as well as cognitive performance were related in at-risk subjects. For rAI–PCC connectivity strength, positive correlation was found with the severity of reported positive-symptom sum-score (comprising symptoms such as unusual thought content, persecutory delusions, grandiosity, perceptional abnormalities, and disorganized communication) (*rho=0.*32). Both the rAI-PCC and MPFC–rDLPFC connectivities were correlated with the SPI-A-subscore of body perception disturbances. These included migrating and electric bodily sensations, sensations of movement, pulling or pressure, sensations of body or parts of it extending, diminishing, shrinking enlarging, growing, or constricting (Schultze-Lutter et al., 2007) (rAI–PCC, *rho*=0.30; MPFC–rDLPFC, *rho*=0.32).

With regard to cognitive functions, all correlations indicated negative associations, meaning that a high coupling was related to poor performance on cognitive tests. The quality of performance on the FAIR was inversely associated with the DMN–TPN connectivity strength (r=–0.38, p=0.01). The time required to solve the problem in the Tower of Hanoi task (r=–0.47, p=0.002) as well as number of moves needed (r=–0.50, p=0.001) were significantly correlated with DMN–TPN coupling strength. Finally, performance on ROCF recall tasks was correlated with the iFC between MPFC and rDLPFC (r=–0.63, p=0.001). None of the measured cognitive functions was correlated with the rAI–PCC iFC. Furthermore, neither age nor CPZ-equivalents was correlated with any connectivity values (p's>0.2).

4.5. Discussion

Our study demonstrated aberrant spatial connectivity patterns for subjects meeting HR or UHR criteria in all three networks.

Intriguingly, the iFC for MPFC–rDLPFC and rAI–PCC, as well as the inter-network connectivity of DMN–TPN, were increased in both at-risk groups compared with CTRL, inferring that the typically observed anticorrelation is absent in the risk-state for psychosis. Notably, those aberrant patterns were associated with symptoms related to reality distortions, and enhanced connectivity strengths of MPFC–rDLPFC and DMN–TPN were related to poor performance in cognitive functions.

Significant differences among the groups for iFC were identified between the MPFC and a single cluster in the rDLPFC (Fig. 1 A1). *Post-hoc* analysis revealed an anticorrelation between the MPFC and the rDLPFC only for CTRL. By contrast, HR showed positive coupling while UHR exhibited no coupling (Fig. 1 A2). The DLPFC is consistently activated during demands for external attention and executive control, e.g., in working memory tasks, whereas MPFC activation is suppressed (Greicius et al., 2003; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003). Associated therewith, the DLPFC forms a core region of the TPN, which, in healthy subjects, is anticorrelated with MPFC activity, i.e., the seed region for the DMN (Fox et al., 2005; Fransson, 2005). The rDLPFC overlapped with the TPN in our control-group (Fig. 1 A1), which is in accordance with prior studies of schizophrenia showing that regions demonstrating greater connectivity with the DMN seed-ROIs in patients overlap with TPN in healthy control subjects (Chai et al., 2011; Whitfield-Gabrieli et al., 2009; Woodward et al., 2011). Additionally, our inter-network connectivity measurements showed that risk groups did not reveal the normal anticorrelation in DMN–TPN (Fig. 2). This analysis was restricted to areas that were the same for all three groups. Therefore, we could confirm that this result was not driven by the aberrant spatial extent of the DMN to the rDLPFC. This finding is consistent with reduced DMN–TPN anticorrelation in subjects at ultra-high risk for psychosis (Shim et al., 2010) or schizophrenia (Hasenkamp et al., 2011; Manoliu et al., 2013; Whitfield-Gabrieli & Ford, 2012).

Whereas Shim et al. (2010) examined averaged iFCs only within DMN and TPN, we additionally demonstrated that the rDLPFC was aberrantly coupled to the DMN in our risk groups. Furthermore, we extended this finding, demonstrating that not only subjects with brief or attenuated psychotic symptoms (UHR) lacked this negative coupling, but also subjects showing only basic symptoms (HR). We therefore inferred that the absence of TPN–DMN orthogonality also underlies subtle disturbances, e.g., sub-clinical self-experienced disturbances in thought, speech, and perception processes, which are clearly distinct from attenuated or frank psychotic symptoms. This TPN–DMN antagonism is believed to reflect the competition between external and internal information processing, with the former suggested to serve goal-directed mental processing and the latter, perceptually decoupled thought (Smallwood et al., 2013). Therefore, a proper functional coordination between these normally anticorrelated networks is considered crucial for cognitive performance (Anticevic et al., 2012; Fox et al., 2005). Correspondingly, increased MPFC–rDLPFC coupling was associated with poor performance in a recall task, in line with a former report showing that increased DMN connectivity is associated with abnormal working memory-related activity in DLPFC (Whitfield-Gabrieli et al., 2009). Furthermore, we found that connectivity strength between the DMN and the TPN was correlated with selective attention and measures of executive functions. However, the association to selective association does not reach significance, when corrected for multiple comparisons. Interestingly, Carhart-Harris et al. (2012) described an increased DMN–TPN iFC in a drug-induced psychedelic state, which may serve as a model of psychosis. Those authors hypothesized that this aberrant coupling underlies "disturbed ego boundaries", as seen in early psychosis, and, therefore, could explain the inability to distinguish between one's internal world and the external environment. Likewise, we found a positive correlation between MPFC–rDLPFC coupling strength and the presence of body perception disturbances, which also occur in drug-induced models of psychosis (Gouzoulis-Mayfrank et al., 2005).

Using the rAI as a seed for the SN (Seeley et al., 2007; Woodward et al., 2011), we found significant spatial differences among the groups for a single cluster in the PCC (Fig. 1 B1). The CTRL revealed an anticorrelation between the rAI and PCC, while HR and UHR showed positive couplings between those regions (Fig. 1 B2). Noteworthy, the PCC forms an integral part of the DMN (Fox et al., 2005) (see also Fig. 1 B1 and S1). This suggested an aberrant overlap between DMN and SN. Interconnectivity measurements showed that differences among groups only trended toward significance, indicating that the SN in the risk groups is characterized by an overlap to their DMN rather than by abnormal inter-network connectivity of the whole SN with the DMN or TPN. Interestingly, the rAI–PCC connectivity strength was not correlated with any cognitive functions but instead with clinical features related to reality distortions, i.e., to positive symptom scores and symptoms in body perception disturbances. Such symptoms have previously been speculated to be associated with rAI disturbances (Palaniyappan et al., 2012). This is further supported by recent data from schizophrenic patients that provide evidence for an association between rAI activity with both, reduced coupling between DMN/TPN and hallucinations (Manoliu et al., 2013). Beyond that, our results suggest that this association is present even in the sub-clinical psychosis state. Structural deficits in the insular cortex have been repeatedly reported in subjects at risk for psychosis (Fusar-Poli, Radua, et al., 2012). In particular, abnormalities in grey matter volumes in the right insula have been linked to higher risks for transition to psychosis (Smieskova et al., 2012). Therefore, it is notable that, even if only trending toward significance, the positive coupling between the rAI and PCC was higher for UHR than for HR (Fig. 1 B2). Because HR criteria are presumed to characterize the early, and UHR, the late, prodromal phase (Fusar-Poli et al., 2013; Klosterkötter et al., 2011), this finding might indicate the risk of developing psychotic symptoms. As we did not find a significant group-difference in MPFC-rDLPFC coupling, it can be speculated that those changes occur early in the disease course (at the HR-state) without a later increase of the coupling

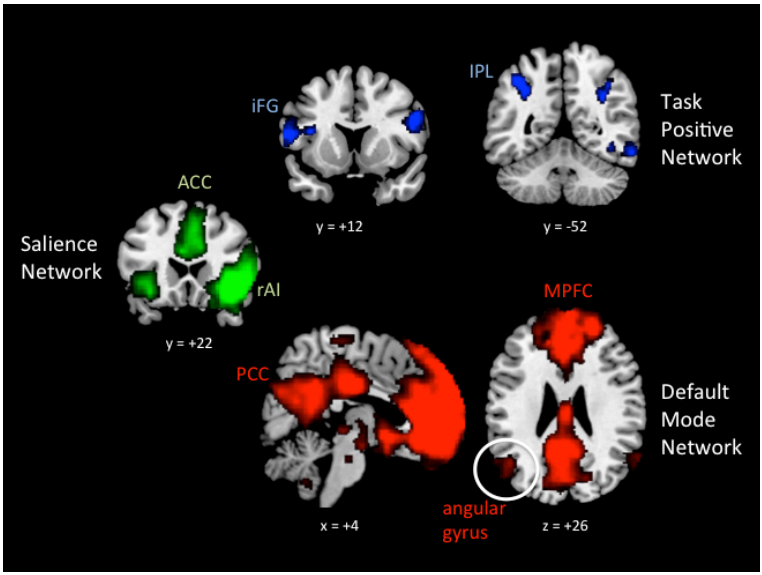
(at the UHR-state). In the rAI-PCC connectivity an increasing coupling occurs during disease progression.

Our findings strongly support the recent theory that SN plays a cardinal role in the development of psychotic symptoms (Palaniyappan et al., 2012; Palaniyappan & Liddle, 2012). Functional deficits in SN potentially lead to excessive salience attribution to internal experiences, which consequently may be responsible for delusions and hallucinations in schizophrenia (Bressler & Menon, 2010; Menon, 2011). A limitation in our study is that, only the correlation between iFC and cognitive variables however, not with clinical variables, survived correction for multiple comparisons. Furthermore, some subjects were medicated, and (antipsychotic) medication contributes to changes in iFC (Sambataro et al., 2010).

In summary, we have identified an association between impaired iFC and cognitive processing as well as symptoms related to reality distortions in the pre-clinical psychosis-risk state. This suggests that abnormal network interactions are involved in disrupting one's capacity to distinguish between the internal world and external environment, eventually leading to a rise in psychotic perceptions. Our findings imply that an aberrant spatial extent in the three networks, and decreased TPN–DMN orthogonality, are important features in the risk-state. This strongly supports the existence of a triple-network model (DMN, TPN, and SN) (Menon, 2011) for the development of psychotic disorders.

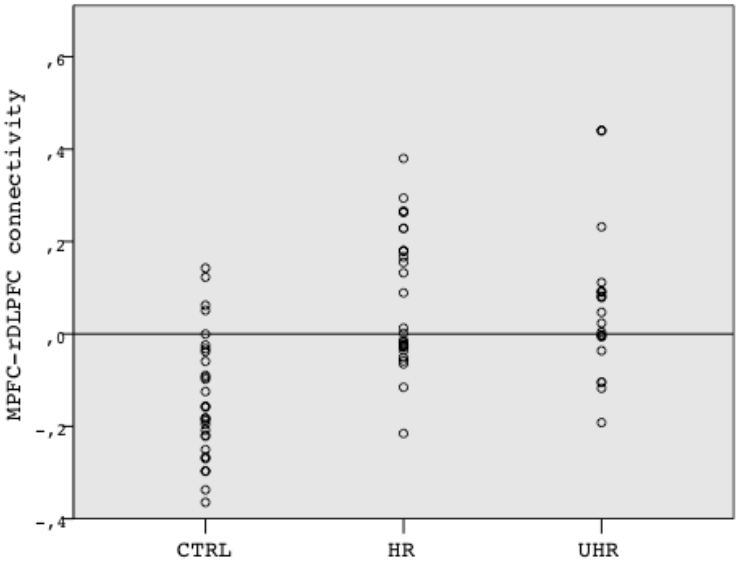
4.6. Supplementary

Figure S1
iFC-masks used for inter-network connectivity



Networks extracted from the healthy control group (n=29) revealed significant clusters within the inferior frontal gyrus (iFG), inferior parietal lobule (iPL) for the task positive network; the posterior cingulate cortex (PCC), the medioprefrontal cortex (MPFC) and the angular gyrus for the default mode network, and the anterior cingulate cortx (ACC) and left and right anterior insular cortex (rAI) for the salience network (whole-brain cluster corrected alpha .05 for voxelwise *p*-value of .001).

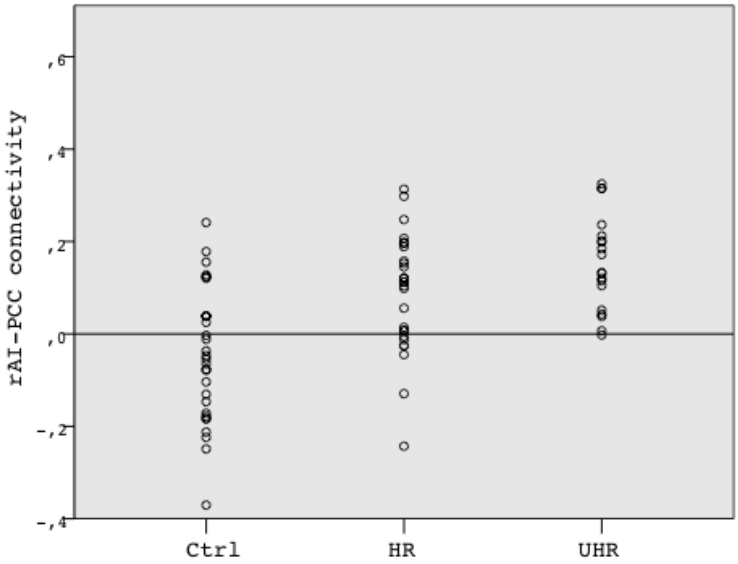
Figure S2
Scatterplot of individual MPFC-rDLPFC connectivity scores.



CTRL showed a significant anticorrelation between the MPFC–rDLPFC connectivity (mean z=–0.14, t=–5.5, p<0.0001, cohen's d=1.08). By contrast, HR, but not UHR, had a positive coupling (mean z=0.08, t=3.0, p<0.005, cohen's d=0.53).

Abbreviations: MPFC: medioprefrontal cortex; rDLPFC: right dorsolateral prefrontal cortex; CTRL: healthy control group; HR: subjects at risk for psychosis; UHR: subjects at ultra-high risk for psychosis.

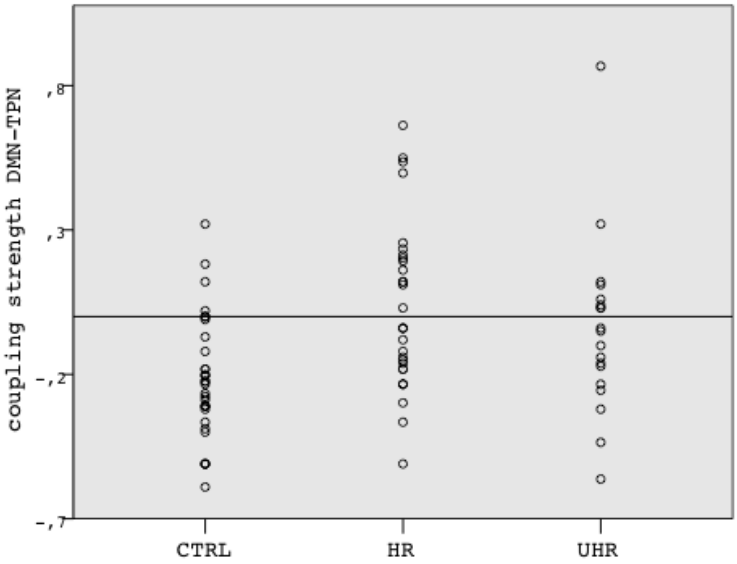
Figure S3
Scatterplots for individual rAI-PCC connectivity scores.



CTRL had a significant inverse coupling between rAI and PCC (mean z=–0.05, t=-2.1, p<0.05, cohen's d=0.33), while the rAI seed was positively coupled with the PCC in both HR (mean z=0.09, t=3.8, p<0.0005, cohen's d=0.69) and UHR (mean z=0.15, t=5.2, p<0.0001, cohen's d=1.5).

Abbreviations: rAI: right anterior insula; PCC: posterior cingulate cortex; CTRL: healthy control group; HR: subjects at risk for psychosis; UHR: subjects at ultra-high risk for psychosis.

Figure S4
Scatterplot for individual coupling strength in DMN-TPN.



Significant anticorrelations were shown between the DMN and TPN in CTRL by post-hoc one-sample t-tests (mean z=-0.21 *t*=–5.2 p<0.0001 cohen's d=0.96). In contrast, neither HR (mean *z*=0.04 *t*=–0.74, *p*=0.46, cohen's d=0.14) nor UHR (mean *z*=0.05 *t*=–0.69, p=0.50, cohen's d=0.16) exhibited significant coupling for DMN-TPN.

Abbreviations: DMN: default mode network; TPN: task positive network; CTRL: healthy control group; HR: subjects at risk for psychosis; UHR: subjects at ultra-high risk for psychosis.

Chapter 5

Study II: Symptom dimensions are associated with reward processing in unmedicated persons at risk for psychosis

5.1. Abstract

There is growing evidence that reward processing is disturbed in schizophrenia. However, it is uncertain whether this dysfunction predates or is secondary to the onset of psychosis. Studying 21 unmedicated persons at risk for psychosis plus 24 healthy controls (HCs) we used a incentive delay paradigm with monetary rewards during functional magnetic resonance imaging. During processing of reward information, at-risk individuals performed similarly well to controls and recruited the same brain areas. However, while anticipating rewards, the high-risk sample exhibited additional activation in the posterior cingulate cortex, and the medio- and superior frontal gyrus, whereas no significant group differences were found after rewards were administered. Importantly, symptom dimensions were differentially associated with anticipation and outcome of the reward. Positive symptoms were correlated with the anticipation signal in the ventral striatum (VS) and the right anterior insula (rAI). Negative symptoms were inversely linked to outcome-related signal within the VS, and depressive symptoms to outcome-related signal within the medial orbitofrontal cortex (mOFC). Our findings provide evidence for a reward-associated dysregulation that can be compensated by recruitment of additional prefrontal areas. We propose that stronger activations within VS and rAI when anticipating a reward reflect abnormal processing of potential future rewards. Moreover, according to the aberrant salience theory of psychosis, this may predispose a person to positive symptoms. Additionally, we report evidence that negative and depressive symptoms are differentially associated with the receipt of a reward, which might demonstrate a broader vulnerability to motivational and affective symptoms in persons at-risk for psychosis.

5.2. Introduction

Subcortical dopamine dysregulation is a cornerstone in our understanding of schizophrenia (Howes & Kapur, 2009). There is general agreement on the central role of dopamine in mediating mesostriatal neural activity involved in reward processing, specifically in encoding motivational value and salience (Bromberg-Martin et al., 2010). Accumulating evidence suggests dysregulated dopaminergic transmission as a possible mediator for disturbances associated with altered processing of reward, incentive salience and learning in schizophrenia (Ziauddeen & Murray, 2010). Both the anticipation and receipt of rewards have distinct neural correlates (Berridge et al., 2009; Dillon et al., 2008; Knutson et al., 2001b). The anticipatory phase involves activation in the ventral striatum (VS), encompassing the nucleus accumbens (NAcc; (Knutson et al., 2001b; Schott et al., 2008) and the anterior insula (Knutson & Greer, 2008; Krebs et al., 2012; Volz et al., 2004). This anticipatory signal has been proposed to code the expected value of the predicted reward probability distribution rather than reward prediction error per se (Schultz, 2010). It is hypothesized that chaotic firing of dopaminergic neurons projecting to those regions mediates inadequate attribution of salience to irrelevant events, which might contribute to the formation of positive psychotic symptoms (Kapur et al., 2005; Palaniyappan & Liddle, 2012). Nielsen et al. (2012) whose study draws upon the concept of anticipation of reward being associated with salience processing, found a significant correlation between striatal activation during this stage to positive symptoms, agreeing with the aberrant salience theory.

During reward feedback, VS activation reflects prediction error in response to unexpected rewards (Schultz, 2002) while activity in the ventromedial/medial orbitofrontal cortex (mOFC) signals the updating of reward value (Grabenhorst & Rolls, 2011) and hedonic experience (Kringelbach, 2005). Accordingly, a deficit in the processing of reward receipt on both levels has been associated with anhedonia and depression, although the findings are more consistent for the VS

than for the mOFC (Gradin et al., 2011; McCabe, Cowen, & Harmer, 2009; Pizzagalli et al., 2009; Simon et al., 2010a). Dysfunctional activation during both anticipation and outcome in striatal and cortical regions has been associated with negative symptoms (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Simon, Biller, et al., 2010a; Waltz, Frank, Wiecki, & Gold, 2011). Some groups including our own have suggested that a higher specificity can be reached by investigating subdimensions of negative symptoms, which was not feasible in the context of this high-risk study.

There is consistent evidence that reward processing and associated cortico-striatal interactions are perturbed in schizo□phrenia (Heinz & Schlagenhauf, 2010; Simon, Walther, et al., 2010b; Ziauddeen & Murray, 2010). Attenuated striatal responses during the anticipation of rewards have been primarily observed in unmedicated patients with schizophrenia (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Schlagenhauf et al., 2009), although medicated patients with more severe negative symptoms also seem to show a reduced signal (Simon et al., 2010a; Waltz et al., 2011). However, it is uncertain whether dysregulations of the reward system predate or follow the development of psychosis. Examining reward processing in at-risk individuals may provide further insight into illness susceptibility and its underlying pathophysiological mechanisms. Results from recent studies with positron emission tomography (PET) have suggested that dopaminergic dysregulation begins prior to the first psychotic episode, and importantly appears predictive of conversion to psychotic illness (Howes et al., 2009; 2011). Furthermore, motivational salience processing and associated responses in the VS (Roiser et al., 2013), as well as reduced activation during loss-avoidance anticipation in pre-psychotic individuals has been observed (Juckel et al., 2012).

Therefore, our goal was to explore functional brain correlates during both anticipation and receipt of rewards and to evaluate their association with symptoms in unmedicated persons at risk for psychosis. We compared the neural activation of HCs with an unmedicated at-risk group by administering a modified version of the

monetary incentive delay task (Abler et al., 2005; Knutson, Adams, Fong, & Hommer, 2001; Simon, Walther, et al., 2010b). Regarding brain-symptom relationships the previous work cited above provides some evidence for differential associations between symptoms reward anticipation and outcome in patients with schizophrenia, although the findings are heterogeneous. Thus, we tested the following hypotheses: (1) positive symptoms are associated with activation of the VS and the anterior insula during reward anticipation, (2) negative symptoms are associated with reduced VS activation during reward anticipation; and (3) depressive symptoms are associated with reduced VS and mOFC activation during processing of rewarding outcomes.

5.3. Methods

Participants

This project consisted of 21 medication-free participants at risk for psychosis (Risk) and 24 healthy controls (HC). Participants were recruited in the region of Zurich, Switzerland, within the frame of a larger study on early detection of psychosis (www.zinep.ch), which was approved by the cantonal Ethic Commission Zurich (E-63/2009) and complies with the Declaration of Helsinki.

For the present study, psychopathology (i.e., positive and negative symptoms) was rated with the Structured Interview for Psychosis-Risk Syndrome (SIPS; (T. J. Miller et al., 2003), the Schizophrenia Proneness Instrument (SPI-A; Schultze-Lutter et al., (Schultze-Lutter et al., 2007), and the Calgary Depression Scale for Schizophrenia (CDSS; (Addington, Addington, & Maticka-Tyndale, 1993). All participants in the Risk group fulfilled inclusion criterion for high-risk status as assessed by the SPI-A, which was met when at least one cognitive-perceptive basic symptom or at least two cognitive disturbances were reported. Six individuals in the Risk group reported at least one attenuated psychotic symptom or brief, limited intermittent psychotic symptom as assessed by the SIPS, and thus fulfilled additionally the

criterion for UHR status. Imaging of the participants was conducted immediately after entry into the ZInEP study before onset of any treatment.

Persons in the HC group were screened with the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) to ensure that none had any history of psychiatric illness. Individuals in the Risk and HC groups did not differ significantly in terms of age, gender, handedness (assessed with the Edinburgh Handedness Inventory; (Oldfield, 1971), and intelligence (estimated by using tests measuring both verbal (Mehrfachwahl-Wortschatz-Intelligenz Test; MWT-B; (Lehrl, 2005) and nonverbal intelligence (Leistungsprüfsystem; LPS-3; (Horn, 1983); Table 1). Exclusion criteria for both groups were age under 16 or over 35 years, contraindications against MRI, neurological illness, and substance abuse.

Table 1 Demographic characteristics and symptom rating

	HC	Risk	Statistical Evaluation
N	24	21	
Gender (f:m)	11:13	6:15	χ^2=1.42, *n. s.*[a]
Handedness(r:l:b)	21:2:1	19:1:1	χ^2=0.23, *n. s.*[a]
Age (years)	23.3 ± 5.0	25.1 ± 5.6	*t*=-1.8, *n. s.*[b]
Estimated intelligence	115.8 ± 14.4	111.6 ± 14.4	*t*=1.0, *n. s.*[b]
SIPS:			
- Positive	-	6.5 ± 3.9	-
- Negative	-	9.8 ± 5.8	-
- General	-	6.6 ± 3.0	-
- Disorganization	-	2.5 ± 2.2	-
GAF	-	58.2 ± 19.0	-
CDSS	-	6.5 ± 2.7	-

Abbreviations: HC, healthy controls; Risk, subjects at-risk for psychosis; r:l:b, r=right l=left b=both/bimanual; SIPS, symptoms according to Structured Interview for Prodromal Syndromes; GAF, Global Assessment of Functioning Scale Mean; CDSS, Calgary Depression Scale for Schizophrenia. [a]Pearson's chi-square test; .[b]2-sample *t*-test; *n.s.*, not significant (p>.05). ±SD where appropriate. Estimated intelligence was based upon mean scores from evaluations of verbal (MWT-B; (Lehrl, 2005) and nonverbal (LPS-3; Horn, 2013) skills.

Experimental Design and Task

We used a modified version of the monetary incentive delay task (

Fig. **1**), which has been proven to be a useful probe of neural responses during reward anticipation and receipt. To minimize learning effects during the fMRI, the MID-task was explained carefully by showing each cue and its meaning to the subjects. Participants had to perform a

practice version of the task containing 10 trials, for which they did not receive payment. They were also shown the money they could earn by performing the task successfully in the scanner. During functional scan acquisition the test subjects engaged in one session with 50 trials. Two levels of reward were possible: 0 Swiss Francs (CHF) or 4 CHF, with a maximum overall win of 60 CHF. A steady rate of reward vs. non-reward across all participants was accomplished by applying a probabilistic pattern, which entailed no reward being paid in 10 pre-defined trials (out of the 25 trials with a potential reward).

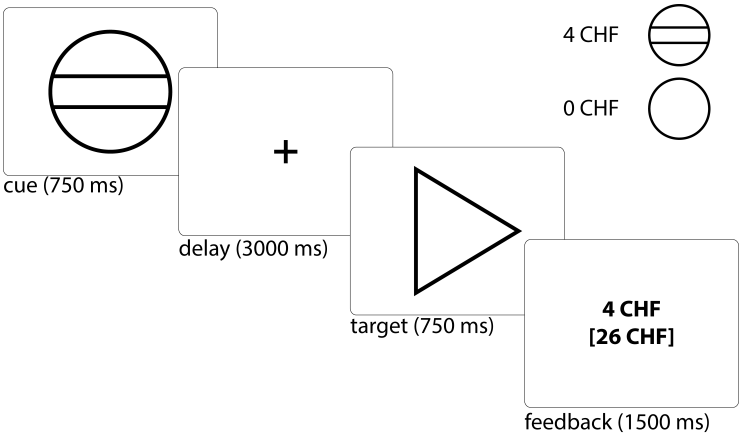


Fig. 1 Monetary incentive delay task: Example trial and cues representing possible reward outcomes. Participants first saw a cue stipulating with an unpredictable probability the amount of money (4 CHF or 0 CHF) they could win, if they reacted correctly within 750 ms during the ensuing discrimination task, which involved pressing either a left or right button depending upon the direction of a triangle after an anticipation period (variable delay: 2500–3500 ms, mean of 3000 ms). Immediately after target presentation, subjects were informed about the amount of money they had won during this trial and their cumulative total win so far (feedback) for a total of 1500 ms (Abler et al., 2005). The jittered inter-trial interval (ITI) was between 1000 and 8000 ms with a mean of 4000 ms. Trial types were randomly ordered.

Imaging data acquisition

Functional and structural MRI was performed at the Psychiatric Hospital, University of Zurich, Switzerland, using a Philips Achieva TX 3-T whole-body MR unit with an eight-channel head coil. Three-dimensional T1-weighted anatomical images were acquired (160 slices; repetition time (TR)=1900 ms; TE=2.2 ms; inversion or echo time (TE)=900 ms; flip angle θ=78°; spatial resolution, 1 × 1 × 1 mm). Functional scans included a T2*-weighted echoplanar imaging sequence (265 volumes; TR=2000 ms; TE=30 ms; 32 contiguous, inter-leaved slices; spatial resolution, 3 × 3 × 3 mm; θ=80°). To minimize susceptibility artifacts in the mOFC, we placed the contiguous axial slices at a 20° angle relative to the anterior-posterior commissural plane. Participants viewed visual stimuli with LCD video goggles (Resonance Technologies). Responses were recorded with a Lumitouch response box (Photon Technologies).

fMRI data analysis

The pre- Our fMRI data were analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The pre-processing steps included realignment, in which fMRI-time series were rigidly registered to a reference image in order to correct for motion artifacts, slice-timing correction, co-registration to a structural T1 scan, spatial normalization to MNI space, and spatial smoothing (8-mm Gaussian kernel). Three of the participants were excluded due to excessive head motion (i.e., linear shift >2 mm, rotation >1°).

A general linear model was constructed for statistical analysis (Friston et al., 1994). Regressors for the two phases of anticipation (expectation of 4 CHF or 0 CHF) and three phases of outcome (receipt of 4 CHF, omission of 4 CHF, or receipt of 0 CHF/neutral outcome) were modeled separately as explanatory variables convolved with the canonical HRF. The six realignment parameters were included together with the onsets of targets and error-trials as regressors of no interest. To examine the anticipation of reward, we contrasted "*anticipation of* 4

CHF vs. *anticipation of* 0 *CHF*". The reward outcome was modeled by contrasting "*receipt of reward* vs. *omission of reward*", i.e., we contrasted outcome regressors for which the preceding anticipation was the same (anticipation of 4 CHF). Thus, although the timing of the task did not allow for a definite separation of the trial phases within the temporal resolution of fMRI, our selection of contrasts nevertheless allowed comparisons between the trial-types of interest.

The individual contrast images were then subjected to a second-level random effects analysis. Within-group activation was compared using a one-sample *t*-test. The initial threshold for group-level maps was $p < 0.001$ (uncorrected). Given our strong *a priori* hypothesis regarding involvement of the VS and rAI in the processing of anticipation rewards and mOFC in the feedback of rewards, we employed family-wise error level correction adjusted for small volume (*P*SVC) across each of our independently derived regions of interest (ROIs) at the voxel level. For the VS, we used anatomical voxel masks for the left and right hemispheres, as retrieved from a publication-based probabilistic MNI-atlas (Nielsen & Hansen, 2002). This method has been used in previous reward-related fMRI studies (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006). For the mOFC, we used a functional ROI based on an earlier reward-related fMRI investigation with healthy participants using the same paradigm (Simon et al., 2010b). Finally, we selected a rAI ROI, because aberrant activation of this brain region has been previously reported in a high-risk sample (Wotruba et al., 2014) and has been suggested to be relevant for the pathomechanisms underlying the development of positive symptoms (Palaniyappan & Liddle, 2012). Importantly, rAI activation has also been shown during anticipation of a reward (Brian Knutson & Greer, 2008; Krebs et al., 2012). We selected a spherical ROI centered on MNI coordinates (x=38, y=22, z=−10; 10 mm radius) (Seeley et al., 2007; Wotruba et al., 2014). The corresponding ROI's are depicted in Fig. 3A, Fig. 4A.

Individual parameter estimates (beta-values) were extracted using the mean of the data, collapsed across all voxels within each ROI using the

REX toolbox (http://web.mit.edu/swg/software.htm), and were correlated to symptom scores (SIPS Negative, SIPS Positive, and CDSS) as well as with RT via Spearman's correlation analysis. Significant results are reported at $p < 0.05$. No correction for multiple testing was applied to the correlational analyses.

In addition, we performed a whole-brain analysis using the aforementioned contrasts to identify group differences in brain areas outside the ROIs. The threshold was set to voxelwise $p < 0.001$ and 20 contiguous voxels, corresponding to a false-positive discovery rate of $p < 0.05$ across the whole brain as estimated by Monte Carlo simulation.

All raw data are available from the corresponding author on request.

5.4. Results

Behavioral results

The average error rate for all subjects was 2.1%. Participants were significantly faster in trials when 4 CHF was promised (mean 379.3 ms, SD 6.7) than when they expected no reward (mean 406.3 ms, SD 5.2; t=3.3, p=0.002). The groups did not differ significantly in either RTs ($p > 0.5$) or error rates ($p > 0.2$).

Anticipation

Within group activations during reward anticipation: We first analyzed within group activations to anticipation of possible rewards (i.e., *anticipation of* 4 *CHF vs. anticipation of* 0 *CHF)* in each of our a priori defined regions of interest. Both HC and Risk groups displayed significant hemodynamic responses within the left VS (HC: z=4.81, PSVC < 0.000; Risk: z=4.62, PSVC =0.004), right VS (HC: z=5.19, PSVC < 0.001; Risk: z=4.79, PSVC =0.003), and rAI (HC: z=4.31, PSVC < 0.001; Risk: z=3.48, PSVC =0.004). Only at-risk persons exhibited activation within the mOFC (z=3.32, PSVC =0.03).

Between group comparisons during reward anticipation: In the a priori defined ROIs (VS, rAI, mOFC) no significant differences between HC and Risk groups were observed. We performed an exploratory whole brain analysis, which revealed significantly increased hemodynamic responses in the Risk vs. HC group within the following regions: posterior cingulate cortex [PCC; Brodmann Area (BA) 31; x=3, y=−45, z=27; cluster size=123 voxels], superior frontal gyrus (SFG; BA 9; x=9, y=57, z=30; cluster size=41 voxels), bilateral medial frontal gyrus (MFG; BA 8; x=30/−24, y=24, z=48/45; cluster size=36/50 voxels) (Fig. 2). Activations were not significantly increased in any brain region for the HC subjects relative to the Risk group.

Correlations between ROI activation and psychopathology: The ROI-based analysis revealed significant correlations between the SIPS positive symptom score and hemodynamic response in the left VS (ρ=0.54, p=0.012; Fig. 3A1) and right VS (ρ=0.59, p=0.005; Fig. 3A2), as well as in the rAI (ρ=0.52, p=0.015; Fig. 3A3). No significant association was found between regional brain activation and negative or depressive symptoms during the phase of reward anticipation.

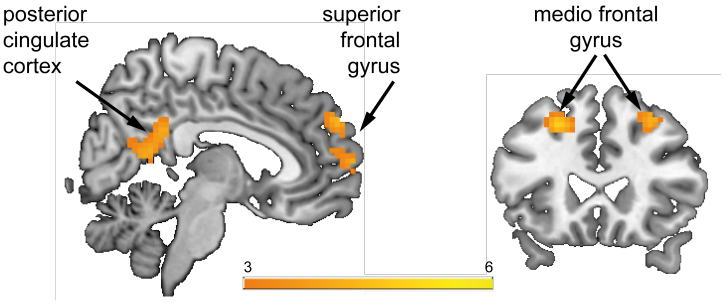


Fig. 2 Whole-brain group comparison of the contrast reward anticipation vs. no reward anticipation. Subjects at risk for psychosis showed significantly stronger hemodynamic response compared to healthy controls in the posterior cingulate cortex, superior frontal gyrus, and bilateral medio frontal gyrus (corresponding t-values are represented in orange/yellow).

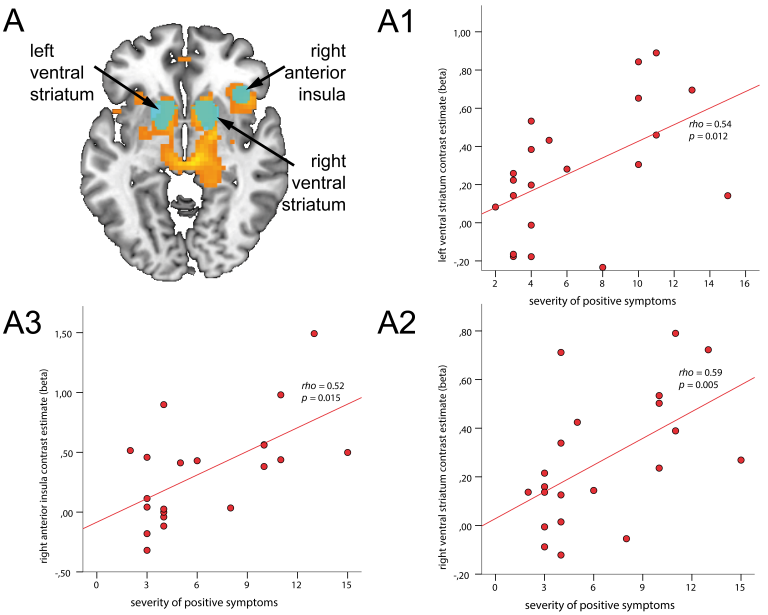


Fig. 3 Associations between regions of interest (ROI) and severity of positive symptoms during anticipation of reward. ROIs (depicted in cyan) are overlaid on within-group t-maps for subjects at risk for psychosis (A) for the contrast reward anticipation vs. no reward anticipation (shown in orange, both at a voxel-wise threshold $p < 0.001$, with an extent of 20 voxels). ROI-based analysis revealed significant association between contrast estimates of the left and right ventral striatum (VS) (A1, A2) and right anterior insula (rAI) (A3) with positive symptom scores ($\rho > 0.52$, $p < 0.015$).

Outcome

Within group activations during reward outcome. We first analyzed the contrast receipt of reward vs. omission of reward in each of our a priori defined regions of interest for each group separately. Both groups showed significant hemodynamic responses within the mOFC (HC: z=4.93, *P*SVC < 0.000; Risk: z=3.33, *P*SVC =0.036), left VS (HC: z=4.80, *P*SVC < 0.000; Risk: z=4.03, *P*SVC =0.002), and right VS (HC: z=4.87, *P*SVC < 0.000; Risk: z=4.55, *P*SVC < 0.000), but not within the rAI.

Between group comparison during reward outcome. No significant group differences were found within the a priori defined ROIs. An exploratory whole brain analysis did not reveal any additional regions with significant between group differences.

Correlations between ROI activation and psychopathology. The ROI based correlations for the contrast receipt of reward vs. omission of reward revealed negative correlations for depressive symptoms with contrast estimates within the mOFC (ρ=−0.46, p=0.037; Fig. 4B1), and for negative symptoms with the left VS (ρ=−0.44, p=0.045; Fig. 4B2). No significant association with positive symptoms could be observed. An additional correlation analysis revealed a significant inverse relationship between RT during the 4 CHF condition and the outcome signal in the left VS (ρ=−0.42, p=0.04) for the HC group but not for the Risk group (Fig. 4C)

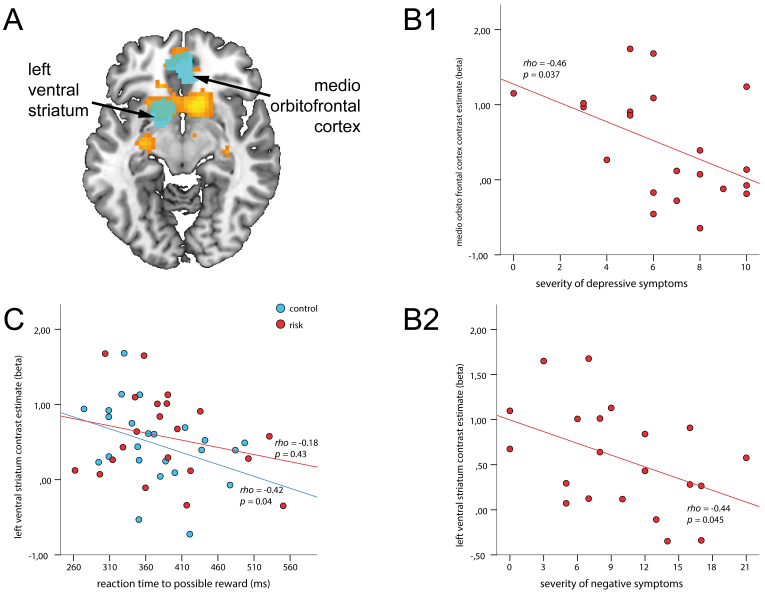


Fig. 4 Associations among regions of interest (ROIs), clinical symptoms, and reaction time (RT) to cues with possible reward during outcome. ROIs (depicted in cyan) are overlaid on the within-group t-map for subjects at risk for psychosis (A) for the contrast receipt of reward vs. omission of reward (shown in orange, both at a voxel wise threshold of $p < 0.001$, with an extent of 20 voxels). ROI-based analysis revealed a negative association between contrast estimates within the medio orbitofrontal cortex and severity of depressive symptoms (B1), and the left VS and severity of negative symptoms (B2) ($\rho > -0.44$, $p < 0.045$). (C) Signal in the left VS revealed a significant inverse association with RT in healthy controls (blue; $\rho = -0.42$, $p = 0.04$) but not for subjects at risk for psychosis (red; $\rho = -0.18$, $p = 0.43$).

5.5. Discussion

In our study, unmedicated individuals at risk for psychosis showed similar error rates and RTs as HCs during a monetary incentive delay task. The task was intended to produce low error rates, which lead both groups to perform at ceiling. Both groups recruited similar brain areas when processing reward information. However, during the anticipation phase, those in the Risk group exhibited additional activation in the PCC, MFG, and SFG. During receipt of rewards, the two groups did not differ significantly. Importantly, the neural processing of anticipation and receipt of rewards was differentially related to symptom dimensions. Positive symptoms were associated with the processing of reward anticipation, while negative and depressive symptoms were related to the processing of a rewarding outcome.

The lack of a significant group difference in the VS during reward processing contrasts with earlier findings from unmedicated patients with schizophrenia (Esslinger et al., 2012; Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Schlagenhauf et al., 2009), in which activation in the VS was diminished during the anticipation phase. This may have been due to variations in experimental designs, i.e., the only previous study employing this monetary incentive delay task in a (partially-medicated) high-risk sample (Juckel et al., 2012), found no group differences in the VS during reward anticipation.

During the anticipation period, higher activation in the SFG and MFG was observed in the Risk group. Therefore, the impending action might have required increased effort to maintain task performance, which led to increased frontal activation. Compensatory hyperactivation of these regions has repeatedly been reported in patients with schizophrenia (Deserno, Sterzer, Wustenberg, Heinz, & Schlagenhauf, 2012; Potkin et al., 2009). Noteworthy, recent findings (Guitart-Masip et al., 2011) show that anticipatory signals capture some aspects of response preparation, which, in turn, may be related to the frontal hyperactivation shown by subjects in the at-risk group.

However, our task does not allow differentiating between response preparation and reward anticipation, which would require future studies. We also found significantly stronger activation in the PCC for the Risk group compared with HC. The PCC is a key node of the default mode network, which, in healthy individuals, activates during rest periods, but deactivates during goal-directed tasks (Fox et al., 2005). Therefore, similar to reports with schizophrenia (Whitfield-Gabrieli & Ford, 2012), our result indicates less task-dependent deactivation of the PCC in the risk state for psychosis.

A central finding of our study is that positive symptoms are correlated with VS and rAI activation during reward anticipation. Dysfunctional activation of VS and rAI has been associated with aberrant assignment of salience to otherwise irrelevant stimuli, which might be part of the neuropathophysiological mechanism leading to psychotic symptoms (Jensen et al., 2008; Palaniyappan & Liddle, 2012). Consistent with this, patients with higher positive symptom scores have been observed to elicit greater hemodynamic responses in the VS to neutral stimuli (Jensen et al., 2008; Roiser et al., 2013; Romaniuk et al., 2010). In contrast, our at-risk participants, with a higher degree of sub-clinical positive symptoms, displayed a stronger signal response to meaningful cues. Thus, individuals with potentially prodromal symptoms might be predisposed to over-attributing salience to *any* event, which might reflect a sign for aberrant salience signaling after the onset of overt psychosis. In contrast to our own results, recent reports with unmedicated schizophrenic patients have pointed to an *inverse* relationship between VS activation and positive symptoms (Esslinger et al., 2012). These different results could be due to the fact, that previous studies employed a salience contrast involving losses while our trials included only reward contrasts.

In addition, a recent report shows that first-degree relatives of patients with schizophrenia show a decrease in VS activation during reward anticipation, which is also influenced by a polymorphism in the neuregulin-1 gene (Grimm et al., 2014). The fact that at-risk participants in our study did not show reduced VS activation in

association with reward anticipation might reflect our different method of identifying individuals with increased likelihood of developing psychotic illness (based on subclinical symptoms rather than genotypes).

We observed an inverse relationship between the severity of negative symptoms and VS activation during the receipt of reward. This finding was somewhat unexpected, because in patients with schizophrenia an association of ventral striatal hypoactivation and negative symptoms was mainly reported for the anticipation phase (Juckel et al., 2006; Simon et al., 2010; Waltz et al., 2010). Nevertheless, dysfunctional outcome processing has also been suggested to be associated with negative symptoms (Strauss, Waltz, & Gold, 2013), although these findings relate to prefrontal cortical regions. In addition, stronger activation of the VS during the reward phase was associated with faster RTs in HC participants, but not in Risk participants. This implies a dysregulation of the VS in subjects at-risk for psychosis that might affect the positive impact of rewarding actions and, consequently, contribute to the development of negative symptoms.

Furthermore, individuals with higher scores for depressive symptoms exhibit less activation within the mOFC, a region involved in immediate and simple hedonic responses (Kringelbach, 2005). Thus, reduced coding of pleasurable experiences in the mOFC may contribute to the neurobiological origin of depressive symptoms in at-risk persons. In contrast to our previous study in patients with schizophrenia, no association between depressive symptoms and VS activation during outcome was observed (Simon et al., 2010a). For both negative and depressive symptoms, one might speculate that individuals with higher symptom scores show less differentiation between positive and negative outcomes due to unregulated dopamine firing (Andreas Heinz & Schlagenhauf, 2010; Schlagenhauf et al., 2009).

A possible shortcoming of the present study is the relatively small sample size. Another constraint is the cross-sectional design, which could limit the relevance of our results. In addition, the correlations

between RT and clinical symptom scores with the hemodynamic response in our ROIs were not corrected for multiple comparisons, which warrant caution in interpreting these findings until independently replicated. In addition, we pooled data from participants fulfilling ultra-high-risk and basic symptom criteria. Therefore, this did not allow us to attribute our findings specifically to either of those types of symptoms. Finally, the relationship between salience, value and reward prediction signals is still a matter of intense debate (Kahnt & Tobler, 2013; Morris et al., 2012). Our task is limited in its capacity to specifically attribute activation during reward anticipation and outcome to one of these signals.

In summary, our results provide evidence for a dysregulation of reward-associated processing in subjects at risk for psychosis, which could be compensated by the recruitment of prefrontal regions. Importantly, higher activation in the striatal and insular regions when anticipating reward-relevant cues might reflect abnormal processing of potential rewarding outcomes. This in turn could lead to a higher risk for developing supra-threshold psychotic disorder, which is in line with the aberrant salience theory of psychosis. Finally, we showed that negative and depressive symptoms are differentially related to VS and mOFC during the receipt of reward. Such a relation may reflect a broader vulnerability for motivational and affective symptoms in at-risk persons.

Chapter 6

General Discussion

6.1. Synopsis

The salience hypothesis of psychosis provides a powerful heuristic framework that can bridge what is known about the dysregulation of dopamine in schizophrenia with the subjective experience of both positive and negative symptoms (Andreas Heinz & Schlagenhauf, 2010; Kapur et al., 2005; Tost et al., 2010; Winton-Brown et al., 2013). However, which of the aspects of salience processing are most crucially altered in the development of psychotic disorders remains unclear. Depending on the nature of how a stimulus is evaluated, two differing concepts have been proposed: (a) the motivational salience hypothesis that states that dopamine mediates the attribution of incentive salience to cues that predict reward, and (b) the proximal salience, which takes place by any stimulus that is conspicuous due to incentive valence, behavioral relevance or expectancy violation (Palaniyappan & Liddle, 2012).

So far, salience processing has been poorly characterized in the pre-psychotic state, especially with regard to symptom dimensions. Thus, the aim of this thesis was to reveal the neurobiological mechanisms of the two aspects of salience processing that could lead to symptoms seen in schizophrenia with two studies using fMRI. In the first study, intrinsic functional connectivity within and between the salience network, DMN and TPN was explored in order to examine whether proximal salience processing is disrupted in individuals meeting early and late potentially prodromal symptoms criteria for psychosis. The second study aimed to investigate motivational salience processing using a delayed incentive paradigm with monetary rewards in an unmedicated sample of individuals at-risk for psychosis.

The findings of each individual study have been discussed in the specific discussion section. In the following, the findings are briefly summarized in the context of the research questions, as outlined in the introduction of the thesis. Furthermore, potential challenges are discussed, resulting in an outlook towards potential future studies that build upon the work begun here.

6.2. Study I

The aim of this study was to explore the concept of proximal salience in the risk-state of psychosis. The concept of proximal salience refers to a momentary state of neuronal readiness generated by any stimulus that is conspicuous due to incentive valence, behavioral relevance or expectancy violation and leads to a change in the brain state. Based on the triple-network theory (Menon, 2011), the proximal saliency is hypothesized to be mediated through the salience network by interacting with the interoceptive pathway and prefrontal system that enables a switching between internally focused mode (DMN) to task-processing mode (TPN) or vice versa.

In schizophrenia, aberrant proximal salience processing refers to the assessment of irrelevant and idiosyncratic external or internal stimuli in the context of interoceptive awareness, which might influence behavior inappropriately (Lena Palaniyappan & Liddle, 2012). This may be caused by a disruption of dynamics between the salience network, the DMN and the TPN. Therefore, proximal salience can be studied indirectly through the analysis of intrinsic functional connectivity within and between the three networks. Indeed, anomalies in coordination between the three networks have been found in schizophrenia (Manoliu et al., 2013; Whitfield-Gabrieli & Ford, 2012), and these, importantly, have been related to reality distortions (Pu et al., 2012; White et al., 2010) .

Based on these findings, the basic idea of this thesis was to determine whether cognitive processes and clinical symptoms associated with the risk-state for psychosis are reflected by aberrant functional connectivity both within and between the DMN, TPN, and salience network. To verify this, rsfMRI was evaluated in three groups of subjects, individuals meeting basic symptoms (HR) and UHR symptoms, as well as a matched group of healthy controls. The rAI was selected as seed region for identifying the salience network; DMN was defined as being correlated positively, the TPN negatively to the MPFC.

The key findings were as follows:

Consistent with earlier findings in schizophrenia (Hasenkamp et al., 2011; Manoliu et al., 2013; Whitfield-Gabrieli & Ford, 2012) as well as in UHR subjects (Shim et al., 2010), we demonstrated that the typically observed antagonistic relationship in MPFC–rDLPFC, and related to this, also the inter-network connectivity of the DMN-TPN, were absent in the two at-risk groups. The rDLPFC forms a core region of the TPN, which in healthy individuals is anticorrelated with activity in the MPFC (Greicius et al., 2003; McKiernan et al., 2003). This TPN–DMN antagonism is believed to reflect the competition between external and internal information processing. Therefore, a proper functional coordination between these normally anticorrelated networks is considered crucial for cognitive performance (Anticevic et al., 2012; Fox et al., 2005). Correspondingly, the functional connectivity measurements here were associated with poor performance in cognitive measurements, but also with presence of body perception disturbances. This latter finding strikingly corresponds with the assumption that a decreased DMN-TPN anticorrelation might drive a breakdown of separateness of one's internal world and external environment as seen in psychosis (Carhart-Harris & Friston, 2010; Carhart-Harris et al., 2012). As a matter of fact, our finding also supports the source monitoring model of schizophrenia, which is based on the idea that psychotic symptoms may emerge from a difficulty distinguishing between the origins of endogenous (i.e., internally or self-generated) and exogenous (i.e., externally or other-generated) stimuli (Nelson, Whitford, Lavoie, & Sass, 2014).

In the context of the salience hypothesis, an interesting finding was that networks of two risk groups were not only characterized by a lack of anticorrelation between the networks, but also by an aberrant spatial extent of the DMN into areas normally belonging to the TPN (i.e. the rDLPFC). As the rDLPFC is normally activated during demands for external attention and executive control, e.g. in working memory tasks, and deactivates under rest, it might be speculated, that this reflects a failure of suppression of attention to irrelevant stimuli. Further, we

revealed that in HR and UHR, the rAI as a seed for this network was positively coupled with the PCC, a key node of the DMN (Fox et al., 2005), while being anticorrelated in healthy controls. Interestingly, this aberrant coupling was not correlated with any cognitive functions, but instead with clinical features related to reality distortions, i.e. positive symptom scores and symptoms in body perception disturbances such as sensations of movement, pulling or pressure, sensations of body or body parts extending, diminishing, shrinking, enlarging, growing or constricting (Schultze-Lutter et al., 2007). The rAI is involved in interoceptive pathways (Menon & Uddin, 2010), while the DMN reflects stimulus-independent, internally directed thought (Anticevic et al., 2012; Fox et al., 2005; Greicius et al., 2003; Gusnard & Raichle, 2001; Mason et al., 2007; Smallwood et al., 2013; Whitfield-Gabrieli et al., 2011)) as well as being implicated as a key structure for both arousal and awareness (for a review consider Leech & Sharp, 2013). Thus, our finding may reflect excessive awareness of internal processes, which in healthy individuals would be unnoticed. This may possibly lead to their externalization in the form of positive symptoms. This supports the notion of the proximal salience being aberrant in the development of psychosis.

However, from the applied approach to studying functional connectivity it is not possible to infer on how these correlations are mediated (see section 2.3, and (Friston et al., 2013). De facto, the psychological content of rsfMRI remains an open question. The DMN, for example, might reflect mind-wandering and day-dreaming, somatic rhythms, introspection, memory and the anticipation of the future or the consolidation and experience of the self - to name only some of the topics of debate (see Callard & Margulies, 2011 for a review).

Furthermore, the model of a disturbed triple-network and proximal salience basically proceeds on the assumption that the rAI has a causal role in the in the recruitment of TPN and DMN, implying a failure of bottom-up processes in psychosis (Javitt, 2009). However, this analysis cannot infer on the direction of functional connection (Friston et al.,

2013). Interestingly, using whole-brain granger causal modeling, Palaniyappan et al. (2013) very recently observed a significant failure of both feedforward and reciprocal influence between the rAI and the DLPFC in schizophrenia. Thus, future studies may confirm whether a failure in the feedforward causal influence from the salience network processing system to the DMN and TPN is present in the risk-state for psychosis.

There are a few methodological issues worth mentioning: First, we here applied the hypothesis driven seed-based approach, raising concerns of whether prior selection of the time series of one sub-region might have biased the definition of our anatomical connectivity maps (see for a review on methodological constraints of rsfMRI analysis Cole, Smith, & Beckmann, 2010). However, resulting networks using this approach are comparable to those from a data driven ICA approach (Rosazza et al., 2012). The main concern is that movement and physiological noise (i.e. heartbeat) sources can potentially induce spurious correlations among voxels, increasing the chance of false positives and confounding the interpretation of our results. However, the groups did not differ significantly in their movement parameters, and by using various steps within the preprocessing pipeline we attempted to deal with the issue of physiological noise as suggested elsewhere (Behzadi et al., 2007; Chai et al., 2012). Furthermore, a main finding of this work was the diminished anti-correlation between networks. Nevertheless, there has been vigorous debate about the true 'negativity' of such between-network relationships. Global mean signal regression is routinely carried out in order to correct for the influence of non-neuronal physiological noise, but might bias towards finding of anticorrelation between the networks (Cole et al., 2010). We therefore did not apply this step in our study. However, the existence of 'true' negative relationships between networks remains a matter of debate (Chai et al., 2012). Furthermore, it remains an open question which factors contribute to the aberrant relationship between networks in individuals at-risk for psychosis. Future studies may include experimental manipulation, for example by using transcranial

magnetic stimulation methods or multimodal approaches. Studies of this kind might also resolve the issue of reverse inference by implying cognitive processes from activation of specific brain states (Poldrack, 2006).

Notwithstanding these limitations, the present data imply that abnormal network interactions in the risk-state for psychosis strongly support the existence of proximal salience playing a role in the development of psychotic disorders.

6.3. Study II

The aim of this study was to explore the concept of motivational salience in the risk-state of psychosis. Motivational salience can be related to reward prediction error (RPE) signals, which encode violations of expectations. These RPEs are known to be encoded by dopaminergic neurons in the mesencephalon and to be projected to the VS (Schultz, 2010). Stimuli that predict reward as well as stimuli, which indicate unexpected reward elicit positive RPEs and therefore phasic dopamine release (e.g. Tobler, Dickinson, & Schultz, 2003). This process is important for reinforcement learning (Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006), but, at least in animal research, has also been associated with the incentive properties of the stimulus itself (Flagel et al., 2011).

Chaotic and stimulus-independent firing of dopaminergic neurons may lead to aberrant motivational salience processing, where an otherwise irrelevant stimulus becomes associated with a motivational value, attracting attention, which might in turn influence behavior inappropriately (Jensen et al., 2008; Kapur et al., 2005; Palaniyappan & Liddle, 2012). Motivational salience can be studied using various reward paradigms focusing on different aspects such as reinforcement learning, incentive motivation or pleasure (Berridge, 2012). Indeed, several lines of evidence indicate that reward processing in schizophrenia is perturbed in cortico-striatal loops. Additionally, different aspects of reward processing have been associated with both

positive and negative symptoms (consider for a review Heinz & Schlagenhauf, 2010; Strauss et al., 2013; Tost et al., 2010; Ziauddeen & Murray, 2010).

However, it is uncertain whether dysregulation of the dopaminergic reward system predate or is secondary to the development of psychosis. Thus, the main goal of Study II was to examine reward processing in individuals at-risk of developing psychosis in order to provide further insight into illness susceptibility and its underlying neuropathophysiological mechanism. Therefore, this study was specifically designed to dissociate brain correlates of anticipation and feedback of reward using the monetary incentive delay task during fMRI in a sample of 21 unmedicated persons at-risk for psychosis and 24 healthy, matched controls. Based on former research, we hypothesized anticipation and outcome of reward being differently associated to pre-psychotic symptoms, that is positive symptoms and negative as well as depressive symptoms.

First, unlike in schizophrenia, where unmedicated patients show a reduction of activation in the VS during reward processing (Beck et al., 2009; Esslinger et al., 2012; Juckel, Schlagenhauf, Koslowski, Wüstenberg, et al., 2006; Nielsen et al., 2012) the at-risk individuals studied here performed equally well as controls and recruited similar brain areas processing reward information, namely VS and rAI activation upon expectation of monetary rewards and VS as well as mOFC activation during receipt versus omission of rewards. However, a central finding was that symptom dimensions were differentially associated with anticipation and outcome of reward. Positive symptoms correlated to the anticipation signal within VS and rAI, while negative symptoms were inversely related to outcome related signal within VS and depressive symptoms within mOFC.

The conclusion was that higher hemodynamic response within VS and rAI to anticipation of incentive cues in persons with higher positive symptom scores might reflect a neural mechanism for aberrant processing of potential future reward that in turn may predispose a

person to aberrant salience processing. In schizophrenia, patients with higher scores in positive symptoms elicited higher hemodynamic response in VS following the presentation of neutral stimuli (Jensen et al., 2008; Roiser et al., 2013; Romaniuk et al., 2010). However, here we provide evidence that individuals with higher degrees of pre-psychotic symptoms also elicited higher signal in response to meaningful cues. This might reflect a latent disposition for aberrant salience processing. In schizophrenia, aberrant salience processing is suggested to result from out-of-context dopamine signaling (Howes & Kapur, 2009; Kapur, 2003; Miller, 1993). Crucially, elevated striatal dopamine synthesis capacity is evident in the at-risk stage of psychosis (Howes et al., 2009) and, importantly, increases during transition to psychosis (Howes et al., 2011). This would support the assumption of different stages in development of aberrant salience processing, beginning with over-attribution of salience to meaningful stimuli and, along with the increase of dopamine–synthesis, the misattribution of salience to neutral stimuli.

Furthermore, given that HR is presumed to reflect an earlier stage than UHR in the development of psychosis, one could assume that HR and UHR would reveal differences in salience processing, depending on the stimuli evaluated. Because UHR symptoms are commonly treated with antipsychotics, we could only include five individuals meeting those criteria, which leads to poor statistical power. Furthermore, the design of the task meant that only meaningful stimuli were assessed. Future studies might include stimuli that feature both relevant and irrelevant stimuli in order to test this hypothesis. PET measurements in the same subjects might show if the presumed qualitative difference in aberrant motivational salience processing is associated with dopamine-synthesis capacity.

Moreover, our data indicate that during anticipation of rewards, the high-risk sample exhibited additional activation in PCC, MFG and SFG. Importantly, we applied a probabilistic reward pattern, which meant that regardless of their performance, no reward was paid out in 10 predefined trials. Thus, the impending action was associated with

an uncertain outcome. Dopaminergic neurons targeting the VS are believed to be a critical for the forebrain circuitry regulating effort-related processes (Salamone, Correa, Farrar, & Mingote, 2007). Hence, the selective frontal activation observed in the risk group might reflect difficulties using internal presentation of motivational goals and lead to higher exertion of effort in maintaining task performance. Notably, behavioral studies employing, for example, serial reaction time tasks in schizophrenia suggest that, similar to our at-risk individuals, reinforcement learning may be relatively intact but accompanied by abnormal neural activation through the use of multiple cognitive processes and neural substrates outside of the striatum (Strauss et al., 2013).

Additionally, the risk group compared to HC revealed significantly greater hemodynamic response to anticipation of reward in the PCC, an area that has been related to subjective value of delayed monetary reward (Kable & Glimcher, 2007) but also forms an integral part of the DMN, which in healthy individuals is greater during rest than when engaging in goal-directed tasks (Fox et al., 2005). Therefore, similar to schizophrenia (Whitfield-Gabrieli & Ford, 2012), our results indicate less task dependent deactivation of the PCC in the risk-state for psychosis. This finding supports the triple-network theory postulating a disruption of proper coordination of networks, which might lead to aberrant saliency mapping (Menon, 2011). Moreover, this finding concurs strikingly with our results in Study I. The presence of enhanced coupling of the rAI with the PCC during rest, and the activation of the rAI together with a fail to 'switch-off' regions within the DMN during the task studied here, support our previous findings of disruption of proper coordination of DMN and the salience network anchored around the rAI (Wotruba et al., 2014).

Furthermore, we provide evidence that negative symptoms are associated with the receipt of reward (i.e. inverse relationship of negative symptoms signal within the VS). The consumption of reward during this stage is thought to produce pleasure, which initiates learning processes that consolidate liking the rewarding goal (Arias-

Carrión, Stamelou, Murillo-Rodríguez, Menéndez-González, & Pöppel, 2010).

Moreover, previous studies have shown that salient stimuli, which predict reward provoke an increase in speed of motor response to obtain the reward (thus can be regarded as a measure of effort or motivation), and importantly, this effect is mediated by dopaminergic signals in the VS (Heinz et al., 1998; Knutson, Adams, et al., 2001). This is in good accordance with our observation of higher signal in VS in healthy controls who reacted faster to cues with potential reward, in contrast to our risk-group that did not show the association between reaction time and activation in the VS. This implies that subjects at-risk for psychosis show similar motivated behavior (i. e. do not differ significantly from controls regarding their reaction time), but a dysregulation of the VS might affect the positive impact of rewarding actions and, consequently, contribute to the development of negative symptoms. However, strictly speaking, it is unjustified to assign a mental process to a different activation of the VS. In order to circumvent the issue of reverse inference (Poldrack, 2008), future studies might include measurements of hedonic impact of the rewards directly in order to correlate such a behavioral measure to reaction time, activation of the VS and negative symptoms.

Additionally, previous studies have shown that VS activation reflects positive prediction-error (D'Ardenne, McClure, Nystrom, & Cohen, 2008), which occurs in the contrast of receipt vs. omission of reward studied here. Thus, it might alternatively be speculated that individuals with higher scores on negative and depressive symptoms show less differentiation between positive and negative outcome (Heinz & Schlagenhauf, 2010; Schlagenhauf et al., 2009). Chaotic dopamine firing is thought to increase 'noise' in the system, which in turn might lead to 'drowning' of dopamine signals associated with cues that indicated reward (Lahera, Freund, & Sáiz-Ruiz, 2013; Roiser, Stephan, den Ouden, Friston, & Joyce, 2010). Thus the salience model also might offer a plausible explanation for negative symptoms. This is to say, incentive stimuli naturally called upon to motivate might be

attenuated by constant aberrant external and internal stimuli which drive the individual to confusion and might lead to negative symptoms such as blunting of affect and decreased ability to initiate thought and ideas.

Accordingly, it might be speculated that a failure of value representation due to chaotic dopaminergic firing reflect the often observed sensory overload during the prodrome to psychosis (Winton-Brown et al., 2013), which might ultimately cause inadequate attribution of salience to stimuli. However, our design was not suited to dissociate whether in the at-risk stage symptoms are related to value signals that are essential to make choices, or to salience signals that are related to attention and arousal. It might be speculated that these two sets of processing are differentially related to positive and negative symptoms.

Furthermore, this functional distinction appears anatomically, depending on the source of dopaminergic innervation. As previously described, dopamine neurons come in multiple types, some encoding value, some motivational salience, both of which are connected with distinct brain networks (Bromberg-Martin, Matsumoto, & Hikosaka, 2010). Value coding dopamine neurons are hypothesized to send their signal to the shell of the NAcc, while salience -coding dopamine neurons send their signal to the core of the NAcc. However, for our correlational analyses of brain activation and symptoms as well as reaction times we extracted the contrast estimates from rather large ROIs. The ROI for the VS for example, encompassed both the shell and the core of the Nacc, as well as parts of the dorsal striatum. Thus we cannot assume that our specified regions were functionally homogenous. In supplemental analysis, we aimed to analyze hemodynamic response within the DS and a smaller ROI for VS as it has been suggested that ventral and dorsal striatum might be associated with differential impairments of reward processing (Heinz & Schlagenhauf, 2010). Indeed, the ventral but not the dorsal part correlated with negative symptoms during outcome (Wotruba et al., in preparation).

There were limitations to the present study. Firstly, the relatively small size of sample, secondly, the cross-sectional design, which limits the understanding of their relevance to the eventual emergence of psychopathology. Finally, we chose the configuration of one run of 50 trials for the fMRI reward paradigm, a configuration shown to be effective for assessing reward related brain function (Knutson, Fong, et al., 2001; Simonet al., 2010) in order to minimize fatigue and habituation. However, this limited the possibility to include more conditions such as different levels of reward.

These limitations notwithstanding, the present results provide compelling evidence of latent dysregulation in motivational salience processing prior to disease onset.

6.4. Limitation and outlook

The present work confirms and extends previous research by investigating the development of psychotic disorders in the context of the salience hypothesis. Nonetheless, these findings gave rise to new research questions. Beside the study specific limitations discussed in the previous sections, a number of caveats need to be mentioned regarding the present work.

The primary aim of this thesis was to establish whether aberrant salience processing in the brain is present prior to overt psychosis, by investigating two concepts, which are hypothesized to reflect different properties of salience processing (i.e. motivational salience versus proximal salience). However, answering this issue has been proven to be quite complex. The first study was so designed that intrinsic functional connectivity could be investigated to explore the concept of proximal salience indirectly. Apart from the aforementioned methodological caveats, it is crucial to note that this might be an issue of inverse inference, as cognitive processes were made upon the activation of specific brain states (for instance, aberrant proximal salience processing upon a disruption of the three networks in Study I, or an attenuated hedonic experience in response to rewards upon a

blunted signal in the VS in subjects suffering from negative symptoms).

In fact, the resting-state terminology itself bears some problematic issues of this kind: the terms 'default mode' and, more crucially, 'salience network', might be biased, as they are made upon linking functional neuroanatomy to the regions found to be functionally connected to psychological content. The term 'default mode network', for example, was made upon the observation that "mysterious, task-independent decreases have (…) frequently been encountered", varying little in their anatomical location, thus "this seems to be a default activity of the brain" (Gusnard & Raichle, 2001 p. 685 and 690).

In this thesis a main focus was put on the two aforementioned concepts of salience processing, however, salience dimensions are multifaceted. By assessing different paradigms, different facets might be studied (i.e. reward prediction, thread prediction, and prediction error by classical conditioning tasks, novelty salience and emotional salience by including items with emotional versus neutral and novel versus familiar scenes, explicit salience attribution by reward learning tasks (Winton-Brown et al., 2013)). Future studies applying these diverse facets should focus on which salience dimensions contribute to the development of psychosis. However, it is important to note that many paradigms are not appropriate in investigating salience processing in subjects at-risk for psychosis. This is due to the fact that some rely upon cognitive processes known to be impaired (see section 1.2), which might confound the results. Thus, approaches to study proximal as well as motivational salience should rely on simple task paradigms. We have accounted for this by employing resting state and the low demands of the monetary incentive delay task.

Although Study I was restricted to resting state, the results of Study I also bear on the interpretation of Study II. Investigating the concept of proximal salience, no correlation could be found between inter-network connectivity and negative symptoms, and the same holds for the anticipation period using the reward paradigm. Strikingly, these

were also the results, where the rAI involvement was apparent, in a key region for proximal salience (Palaniyappan & Liddle, 2012). It might be inferred that this kind of processing reflects the vulnerability to positive symptoms, while the outcome of reward is associated with negative symptoms. This intriguing notion might be studied by multivariate pattern analysis, and might further provide a possible approach to use the imaging together with behavioral data to develop a biological marker for psychotic disorders.

Another limitation of both studies was the sample size. Specifically, in Study II a low statistical power might have restricted us from detecting additional group differences. Thus, a higher sample size should be investigated in future.

Further, to our knowledge, Study I was the first study comparing neuroimaging data between HR and UHR. Results revealed that the aberrances in intrinsic functional connectivity were somewhat less pronounced in HR compared to UHR, which implies that these diagnostic criteria might be associated with differences in symptom burden. This bears important implication for future studies. By defining homogenous subgroups, different facets of symptom dimensions might be analyzed and might confirm differences in neurobiological features and outcome (i.e. by comparing individuals with subthreshold psychotic symptoms such as APS to individuals with only basic symptoms). Comparing individuals with a genetic risk for developing psychosis compared to clinical at-risk symptoms might provide to be useful to explore whether the aberrances are of a trait or a state nature.

Motivational as well as proximal salience processing is hypothesized to be crucially linked to dysregulation of dopamine. However, the present work cannot make specific conclusions about the role of dopamine. Thus, as mentioned above, future studies may involve PET measurements in order to link dopaminergic dysfunction and altered salience processing in people with psychosis.

Concerning the present work it has to be mentioned that in addition to rsfMRI-, task-data, and neuroanatomical data, we collected data for various cognitive functions, as well as arterial spin labeling, diffusion tensor imaging in more than 200 subjects at-risk for psychosis. Hence, this gives us the opportunity for follow-up studies in take on a multi-method perspective. Further, as also longitudinal data were collected, additional analysis would allow for example to compare individuals who develop a psychotic disorder with those who do not.

Regarding the clinical implications of the present findings, various treatment options might be considered. The results of Study I suggest therapies such as body oriented psychological therapy, which aims to foster a coherent sense of embodied self (Röhricht, Papadopoulos, Suzuki, & Priebe, 2009), or mindfulness training which is present in various psychological therapies and meditation approaches (Palaniyappan, White, & Liddle, 2012). Our results of Study II imply that a dysregulation of dopamine might be already present in the risk-state for psychosis, suggesting the use of antipsychotic medication. However, Study II also shows that less activation in mOFC and VS is associated with negative and depressive symptoms, thus such medication might also prove to be problematic, because it may in fact dampen the activity even more and consequently worsen these symptoms (Gardner, Baldessarini, & Waraich, 2005).

In conclusion, we might quote William James who wrote 1890 that "[b]odily experiences, therefore, and more particularly brain-experiences, must take a place amongst those conditions of the mental life of which Psychology need take account. […] Our first conclusion, then is that a certain amount of brain physiology must be presupposed or included in psychology." While crucial importance comes to epidemiology, cognitive psychiatry paradigms and to phenomenological psychopathology, the application of neuroimaging methods has indeed brought an enormous wealth of knowledge in understanding of the pathophysiological mechanisms of psychotic disorders, but much remains to be learned.

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Ziauddeen, H., & Murray, G. K. (2010). The relevance of reward pathways for schizophrenia. *Current Opinion in Psychiatry*, *23*(2), 91–6.

Curriculum Vitae

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Education

05/2010 – 03/2014	PhD studies in Psychology, Doctoral Program Psychology (University of Zurich)
09/2004 – 03/2010	Lic. phil. (Master's degree of Science (M.Sc.)) in Psychology, University of Zurich, Switzerland Major in Neuropsychology, Minor in Biology ▪ Masterthesis on "Die kortikale Netzwerkarchitektur von Graphem-Farb-Synästheten: eine graphentheoretische Analyse" (published, summa cum laude) ▪ Bachelorthesis on "Die Freiheit des Willens, eine Illusion? Kritiken und Kontroversen zum Experiment von Libet, Gleason, Wright und Pearl (1983)". (summa cum laude)
2004	Federal matriculation certificate (eidg. Matura), AKAD College, Zurich ▪ Focus: Economy & Law
2000	Certificate of competence in Business Administration, KLZ, Zurich

Professional Experience

since 05/2013	Collegium Helveticum, University of Zurich und ETH Zurich **Research Associate and Project leader** Psychopharmacological investigation of psychotic like symptoms ▪ Project lead (e.g. establishing novel methodical concepts for studying subjects with psychotic like symptoms, controlling and coordination of the project process) ▪ Planning, realization, and analysis of functional Magnetic Resonance Imaging as well as Positron Emission Tomography- data ▪ Publication of results in scientific journals and conferences

04/2014 – 04/2015	Clinic for Neuroradiology, University Hospital, Zurich
	Research Associate
09/2006 – 06/2011	Institute for Psychology, Department for Neuropsychology, University of Zurich
	▪ Neuropsychological and traffic psychological assessment ▪ Examination and analysis of neuropsychological and traffic psychological testing ▪ Writing expert appraisals ▪ Organization, Optimization and coordination of the project process
06/2006 – 03/2010	Center for Sleepmedicine, Schlaflabor Fluntern
	Lab- & Clinical Assistance ▪ Diagnostic evaluation and therapy of sleep disorders • Polysomnographic examination, CPAP-adjustment, conducting Mutiple Sleep Latency Tests
09/2008 – 02/2009	Institute for Psychology, Department for Neuropsychology, University of Zurich
	Research Assistance ▪ Analysis of Magnetic Resonance Imaging data • Assistance during scientific experiments
06/2008 – 09/2008	Psychiatric University Hospital Charité at St. Hedwig Hospital, Berlin
	Clinical assistance, Traineeship ▪ Assistance in individual- and group therapy ▪ Psychometric tests and anamnestic surveys • Training in psychotherapeutic and psychiatric topics
02/2007 – 05/2007	Psychiatric University Hospital, Neuropsychopharmacology & Brain Imaging, Zurich
	Traineeship ▪ Development and organization of an SQL-data base ▪ Analysis of psychometric data ▪ Assistance during scientific experiments (PET- and EEG)

06/2007 – 07/2007	Homburger Anwälte, Zurich
	▪ Editing legal texts in German and English
	• Database organisation and coordination
01/2006 – 12/2006	Pädagogische Hochschule, Thurgau
	• Transcription of interviews for research purposes
01/2001 – 08/2002	Orbitex Finanz AG, Zürich
	• Processing of subscription and redemption orders of investment products
	• Troubleshooting between bank, trustee and administrator
	• Monitoring and coordination of pricing and data on information systems such as Micropal, Lipper and Bloomberg
	• Correspondence in English and German and organizational responsibilities
2000	WW.FG, Zürich
	• Administrative work and organizational responsibilities and sales support

Teaching

since 2011	Seminar for graduate students: Journal Club in Imaging Neuroscience at the Medical Faculty, Zurich
since 2011	Block course for graduate students: Neuroimaging at the Medical Faculty
04/2015	Block course: Neurobiologie psychischer Störungen (Neurobiology of psychiatric diseases), Advanced Studies in Neuropsychology (DAS), at the Instiute for Psychology, Neuropsychology, Zurich
05/ 2015	Block course: Neurobiologie psychischer Störungen (Neurobiology of psychiatric diseases), Schoresch Kompetenzzentrum für Neurofeedback, Wetzikon, Zurich

2015	Seminar for graduate students: Neurobiologie psychischer Störungen (Neurobiology of psychiatric diseases) at the Institute for Psychology, Neuropsychology, Zurich
05/ 2014	Block course: Neurobiologie psychischer Störungen (Neurobiology of psychiatric diseases), Schoresch Kompetenzzentrum für Neurofeedback, Wetzikon
2014	Seminar for graduate students: Neurobiologie psychischer Störungen (Neurobiology of psychiatric diseases) at the Institute for Psychology, Neuropsychology, Zurich
2011	Seminar for graduate students: Neurobiologie psychischer Störungen (Neurobiology of psychiatric diseases) at the Institute for Psychology, Neuropsychology, Zurich

Supervision of Bachelor- and Master Theses at the University of Zurich

2012	Second advisor of master thesis: *Intrinsic functional connectivity in adolescents at risk of psychosis*. Lilian aus der Au, first advisor: Prof. L. Jäncke
2012	Mentorship for the Masterthesis*: Is the Default Mode Network a neural correlate of 'ego depletion'?*. Barbara Haegi, first advisor: Prof. B. Rasch
2012	Bachelorthesis: *Stellen die bildgebenden Verfahren die Psychopathologie der Schizophrenie auf den Prüfstand?* Simone Lafos, first advisor: Prof. L. Jäncke
2012	Bachelorthesis: *Schizophrenie: eine Diskonnektionsstörung?* Simone Blaser, first advisor: Prof. L. Jäncke
2011	Bachelorthesis: *Das spirituelle Gehirn: Neurobiologische Erklärungsansätze von spirituellem Erleben*. Nicole Bissegger, first advisor: Prof. L. Jäncke
2011	Bachelorthesis: *Die Rolle des Hippocampus bei erhöhtem Risiko einer schizophrenen Psychose:* Bettina Steiger, first advisor: Prof. L. Jäncke

Honours and achievements

05/2013	Travel grant from Schweizerische Akademie der Geistes- und Sozialwissenschaften
03/2013	Trainee Abstract Award for the 2013 Organization for Human Brain Mapping (OHBM) Annual Meeting, Seattle, USA
03/2013	Travel grant from the Department of Psychology, University of Zurich
02/2013	Volker Henn Award for best poster at the 17th Annual Meeting of the Swiss Society of Neuroscience, Geneva, Switzerland
since 2012	Ad hoc Reviewer for Human Brain Mapping, Schizophrenia Bulletin, Frontiers in Human Neuroscience, Schizophrenia Research, and Biological Psychiatry

Languages

German	1st mother tongue
Czech	2nd mother tongue
English	fluent, spoken and written, Level C1 ELP
French	fluent, spoken and written, Level C1 ELP
Italian	Beginner, Level A2 ELP

Scientific publications & presentations

Articles in peer-reviewed journals

Gerstenberg M, Traber-Walker N, Franscini M, Theodoridou A, **Wotruba D**, Metzler S, Müller M, Dvorsky D, Correll CU, Walitza S, Rössler W, Heekeren H. *Adolescents and adults at clinical high-risk for psychosis: Age-related differences in attenuated positive symptoms syndrome prevalence and entanglement with basic symptoms.* Psychological Medicine (2015).

Wotruba D., Heekeren K., Michels L., Buechler R., Simon J.J., Theodoridou A., Kollias S., Roessler W., Kaiser S. *Symptom dimensions are associated with reward processing in unmedicated persons at risk for psychosis.* Frontiers in Behavioral Neuroscience (2014).

Wotruba D., Michels L., Buechler R., Theodoridou A., M. Gerstenberg, Kollias S., Roessler W., Heekeren K. *Aberrant coupling within and across the default-mode, task-positive, and salience network in subjects at risk for psychosis.* Schizophrenia Bulletin (2014).

Haenggi J., **Wotruba D**., & Jaencke L. *Globally altered structural brain network topology in grapheme-color synaesthesia.* Journal of Neuroscience (2011).

Talks

Larger jiittering of brain states in the pre-psychotic brain (11/2015). Special Seminar, Institute of Radiology, UniversityHospital, Zurich, Switzerland

Functional Connectivity Patterns in the prepsychotic brain (09/2015). 5th European Conference on Schizophrenia Research, Berlin, Germany

Neuroimaging in Psychiatry: An objective glimpse into the patients subjective world? (05/2015). Addis Ababa University, Department of Psychiatry, Addis Abeba, Ethiopia

Neuroimaging in Psychiatry: An objective glimpse into the patients subjective world? (05/2015). Public Lecture, University of Gondar, Gondar, Ethiopia

Disturbed functional connectivity patterns in the pre-psychotic state (11/2014). Klinisches Neurozentrum (KNZ), UniversityHospital, Zurich, Switzerland

Resting state fMRI in subjects at-risk for psychosis (05/2014). Institute of Psychology, Neuropsychology, Zurich, Switzerland

Aberrant coupling in resting-state fMRI of people at-risk for psychosis (04/2014). Psychosis Studies Meeting, King's College, London, UK

Functional Neuroimaging in Psychotic Disorders (11/2013). Neuroradiologisches Kolloquium, UniversityHospital, Zurich, Switzerland

Moderne Bildgebungsmethoden als Tor zur subjektiven Realität? (12/2012) Workshop Lehrehrausbildungstag, Kantonsschule Zürich Oberland, Wetzikon, Switzerland

Neurobiological Aspects of the Prodrome to Psychosis (06/2012). Retreat of the Neuroscience Center Zurich (ZNZ),Valens, Switzerland

Funktionelle Bildgebung psychotischer Erkrankungen 04/2012. Kolloquium für klinische und experimentelle Neuropsychologie (KLINEX), UniversityHospital, Zurich, Switzerland

Funktionelle Konnektivität im Resting-state-fMRI bei erhöhtem Risiko für eine psychotische Erkrankung (12/2011). Tag der Forschung der Psychiatrie und Kinder- und Jugendpsychiatrie, University Hospital of Psychiatry, Zurich, Switzerland

Functional Neuroimaging in Psychiatric Diseases (11/2011). Neuroradiologisches Kolloquium, UniversityHospital, Zurich, Switzerland

Resting State bei Probandinnen und Probanden im Risikozustand für eine psychotische oder bipolare Störung (06/2011). Forschungsmeeting, University Hospital of Psychiatry, Zurich, Switzerland

Neurobiologische Korrelate von Frühformen der Psychose (03/2011). Within the framework of the Brainfair, organized by the Neuroscience Center Zurich (ZNZ), Kantonsschule im Lee, Winterthur

Conference presentations

Wotruba D., Heekeren K., Michels L., Buechler R., Simon J.J., Theodoridou A., Kollias S., Roessler W., Kaiser S. *Symptom dimensions are differentially associated with reward processing in unmedicated persons at risk for psychosis.* (2014). 1st Burghölzli Psychiatry Meeting, Zurich

Wyss T., Unterrassner L., Krummenacher P., **Wotruba D,** Brugger P., Haker H., Folkers G., Rösser W., *Increased Pattern Detection in Meaningless Noise of Healthy People with Exceptional Experiences*. (2014) Computational Psychiatry Conference, Zurich

Wotruba D., Heekeren K., Michels L., Buechler R., Simon J.J., Theodoridou A., Kollias S., Roessler W., Kaiser S. *Neural correlates of reward processing in unmedicated persons at-risk for psychosis.* (2014). 4rd Biennial Schizophrenia International Research Conference Meeting (SIRS), Florence, Italia

Unterassner L., Wyss T., Krummenacher P., **Wotruba D**., Brugger P., Haker H., Folkers G., Rössler W. *Increased Pattern Detection in Meaningless Noise of Healthy People with Exceptional Experiences* (2014). 4rd Biennial Schizophrenia International Research Conference Meeting (SIRS), Florence, Italia

Wyss T., Unterassner L., Krummenacher P., **Wotruba D**., Brugger P., Haker H., Folkers G., Rössler W. *Exceptional Experiences in Healthy people - early warning signals of Psychosis?* (2014). 4rd Biennial Schizophrenia International Research Conference Meeting (SIRS), Florence, Italia

Gerstenberg M., Theodoridou A., Traber-Walker N., Franscini D., **Wotruba D**., Metzler S., Dvorsky D., Correll CU., Walitza S., Roessler W. *Frequency and characteristics of the Attenuated Psychosis Syndrome and delineation to other risk profiles in a sample of help-seeking individuals* (2014). 4rd Biennial Schizophrenia International Research Conference Meeting (SIRS), Florence, Italia

Wotruba D., Büchler R. Michels L., Theodoridou A., Gerstenberg M., Kollias S., Roessler W., Heekeren K. *Aberrant coupling between default mode, task positive and*

salience network in psychosis risk-state. (2013). 19th Annual Meeting of the Organization for Human Brain Mapping (OHBM), Seattle, USA.

Wotruba D., Büchler R., Michels L., Theodoridou A., Gerstenberg M., Kollias S., Roessler W., Heekeren K. *Intrinsic connectivity reveals aberrant coupling between major functional networks in the risk-state for psychosis* (2013). Annual Meeting of the Swiss Society of Neuroscience (SNS), Geneva

Wotruba D., Michels L., Büchler R., Theodoridou A., Kollias S., Roessler W., Heekeren K. *Aberrant salience-network connectivity in the pre-psychotic period* (2012). 3rd Biennial Conference on Resting State Brain Connectivity, Magdeburg, Germany

Wotruba D., Michels L., Thedoridou A., Kollias S., Roessler W., Heekeren K. *Increased salience-network in subjects at risk for psychosis; a resting-state-fMRI study* (2012). 3rd Biennial Schizophrenia International Research Conference Meeting (SIRS), Florence, Italia

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…Through the unknown, unremembered gate
When the last of earth left to discover
Is that which was the beginning;
At the source of the longest river
The voice of the hidden waterfall
And the children in the apple-tree
Not known, because not looked for
But heard, half-heard, in the stillness
Between two waves of the sea.
Quick now, here, now, always--
A condition of complete simplicity
(Costing not less than everything)
And all shall be well and
All manner of thing shall be well
When the tongues of flames are in-folded
Into the crowned knot of fire
And the fire and the rose are one.

T. S. Eliot, 1942